

# SIV and SHIV CTL Epitopes Identified in Macaques

Todd M. Allen and David I. Watkins

Wisconsin Regional Primate Research Center, 1220 Capitol Court, Madison, WI 53715, USA

There is accumulating evidence to suggest a key role for CTL in the containment of HIV and SIV infections. As such, there is considerable interest in developing vaccines designed to induce virus-specific CTL responses. Various macaque species, most notably the rhesus macaque, have been used extensively to study AIDS virus pathogenesis and vaccine efficacy. As a result of these studies a number of SIV and SHIV CTL epitopes, and their restricting MHC class I molecules, have been identified. Accurate definition of these CTL epitopes, however, is critical both to the development of vaccines as well as to the construction of MHC class I tetrameric complexes which have revolutionized our ability to measure CTL responses to individual CTL epitopes. In the list provided below, only the Mamu-A\*01 restricted CTL epitopes have been optimally defined through the use of peptide dilutions and knowledge of Mamu-A\*01's peptide binding motif. The other epitopes listed in Table I have been identified through the use of overlapping peptides, however, their optimal lengths have yet to be determined. In Table II additional CTL epitopes are listed for which the restricting MHC class I molecules have yet to be identified. Furthermore, the majority of these epitopes have only been mapped using overlapping 20mer peptides. It will be important to define both the restricting MHC class I molecule of these epitopes and their optimal length if they are to be considered for use in vaccination trials or tetramer construction. The expansion of this list will be very important to studies designed to examine the role of CTL in AIDS virus infections and the effectiveness of CTL-based vaccines. Please contact us with any additional contributions to this list.

Bette Korber	Todd M. Allen	David I. Watkins
phone: 505-665-4453	608-265-3381	608-265-3380
fax: 505-665-3493	608-263-4031	608-263-4031
email: btk@t10.lanl.gov	tallen@primate.wisc.edu	watkins@primate.wisc.edu

**Table 1 Defined CTL Epitopes with Known Restricting MHC class I Molecules**

Virus	Protein Epitope	Restricting MHC		Reference
		Class I Allele <sup>1</sup>	Acc. No.	
SIVmac251	Gag	CTPYDINQM	Mamu-A*01	U50836 Miller, et al. 1991
SHIV	Env	YAPPSGOI	Mamu-A*01	U50836 Allen, et al. 1998
SHIV	Pol	STPPLVRLV	Mamu-A*01	U50836 Egan, et al. 1999
SIVmac251	Env	YNLTKCR	Mamu-A*02	U50837 Watanabe, et al. 1994
HIV-1	Env	KPCVKLTP	Mamu-A*08	Voss, et al. 1996
SIVmac251	Env	EHTPIGLAP <sup>2</sup>	Mamu-B*01	U42837 Yasutomi, et al. 1995
HIV-1	Env	NNLLRAIFA	Mamu-B*12	Voss, et al. 1996
SIVmac32H-15	Gag	SVDEQIQWM	Mafa-A*02	Geretti, et al. 1997

<sup>1</sup>MHC Class I allele designations: Rhesus macaque (*Macaca mulatta*) Mamu; cynomolgus macaque (*Macaca fascicularis*) Mafa

<sup>2</sup>Note: We have been unable to detect responses to this CTL epitope in Mamu-B\*01 defined, SIV infected rhesus macaques (Allen, et al. unpublished observations)

**Table 2 CTL Epitopes without Defined Restricting MHC class I Molecules**

Virus	Protein Epitope	Restricting MHC Class I Allele	Reference
SIVmac251	Nef	GLEGIVYSAR	unknown
SIVmac239	Env	CNKSETDRW	unknown
SIVmac251	Nef	DWQDYTSGPGRYPK	unknown
SIVmac251	Nef	LRAMTYKLAIDMSHF	unknown
SIVmac251	Nef	GIRYPKTFGWLWKLIV	unknown
SIV	Gag	SYVDRFYKSLRAEQTD	unknown
		AAVK	unknown
SIVmac251	Env	YCTLYVTVFY	unknown
	Env	SCRMMETQTSTWFGF	unknown
		NGTR	unknown
	Env	GRDNRITISL	unknown
	Env	RRPGNKTVLPVTIMSG	unknown
		LVFH	unknown

	10	20	30	40	50	60	70	80	90
Gag 251	MGARNNSVLSGKKADELLEKIRLRPGGKKKYYMLKHHVWAANELDRFGLAE SILHKEGCGKILSVLAPLVP TGSSENLKSLYNTVCVIMCIHA								
Gag 239	--V-----N-----								
Gag 251	100	110	120	130	140	150	160	170	180
Gag 239	-----T-----								
Gag 251	EKKVKHTEFAKQIVQRHLVVEGTGTAETMPKTSRPTAPSSSGGGNYPVQQIGGNVYHLLPLSPRTLNAWVKLIIEKKFGAEVYVDFGQALLSEG								
Gag 239	-----								
Gag 251	190	200	210	220	230	240	250	260	270
Gag 239	-----								
Gag 251	CTPYDINQMLNCVGDHQAAMQIIRDIINEEADWDLQHPQAPQQGQLREPSGSDIAGTTSVYDEQIQMWMYRQQNP I PVGNIT YRRW IQLG								
Gag 239	-----								
Gag 251	280	290	300	310	320	330	340	350	360
Gag 239	-----								
Gag 251	LQKCVRMVNPITNIIDVKQGPEKPFQSYVDRFYKSLRAEQTDAAVKNMWTTQTLIIQANPDCKLVLKGLGVNPTLLEMLTACQGVGGPGQK								
Gag 239	-----								
Gag 251	370	380	390	400	410	420	430	440	450
Gag 239	-----								
Gag 251	ARLMAEALKEALIAVPVIPFAAAQKRGRPKRIKWNCGKEGHSARQCRA PRRQGCWKCGKMDHVMACPDROAGFLGLGPWGKKPRNFPWA								
Gag 239	-----Q-----								
Gag 251	460	470	480	490	500				
Gag 239	-----M-----								
Gag 251	QVHQGLTPTAPDEPDAVDLILKNYMQLG...KQQRESREKPYKEVTEEDLILHNSLFGDDQ								
Gag 239	-----REKQ-----								

Figure 1a. Gag CTL Epitopes

SIV and SHIV Epitopes

Pol 251	VLELWEGTLCKAMQSPKKTGMLMWMKNGPCYGQMPRQGTGFRFRPWSMGKARQFPHGSSASGADANCSPRGSSAKELHAVG...QAAR	10	20	30	40	50	60	70	80	90
Pol 239	M-----R-----									ERKA-----
Pol 251	KQREALQGGDRGFAPRQFSLMWRPVTVAHIEGQPVVELLDTGADDSIVTGETLGPHTYTPKIVGGIGGFINTKEYKNVKIEYLGRRIKGTI	100	110	120	130	140	150	160	170	180
Pol 239	-----									F-----
Pol 251	MTGDTPIPIFGRRNLLTALGMSLNLP IAKVVEPKVTLKPGKVPKIQWPLSEKERIVALREICEKMEKDGLLEAPRTNPNYPTFAIKKK	190	200	210	220	230	240	250	260	270
Pol 239	-----F-----A-----D-----									
Pol 251	DKNKWRMLIDFRRLNRVTQDFTFVQLGIPHEAGLAKRKRITVLDIGDAYFSIPLDEFRQYTAFTLP SVNNAEPGRYIYKVLPRQGWKGS	280	290	300	310	320	330	340	350	360
Pol 239	-----									
Pol 251	PAIFQYTMRHVLEPERFKANPDVTLVQYMDLIIASDRTDLEHDRVVLQLKELLNSIGFSTPEEKFOKDDPFQWMMGYELWPTKWLQKIEL	370	380	390	400	410	420	430	440	450
Pol 239	-----S-----									
Pol 251	PQRETWTVNDIQKLVGLINWMAQIYPGIKTKHLQRLIRGKMLTTEEVQWTMAEAEYEENKIIISQEQEGCYQEGKPLEAFVIKSQDNQ	460	470	480	490	500	510	520	530	540
Pol 239	-----									
Pol 251	WSYKIHQEDKILKVGKFAKIKNTHNTGVRLLAHVIQKIGKRAIVIWGQVPRFHLRVERDWEQWTTDYOQVTWIPEWDFISTPPLVRLVLF	550	560	570	580	590	600	610	620	630
Pol 239	-----K-----									
Pol 251	NLVKDPIDEGEFTYYTDGSCNKRQSEKAGAYITDRGKDKVKVLEQTTNQDALEAFIMALTDSGPKTNIIVDSQYVMGIITGCPTESESR	640	650	660	670	680	690	700	710	720
Pol 239	-----A-----									
Pol 251	VNQIIEEMIKKSEIYVAVWVPAHKGIGGNQETDHLVVSQGIROVLFLEKIEPAQEEHDKYHSNVKELVLFKGLPRIVARQIVDTCDKCHKQKG	730	740	750	760	770	780	790	800	810
Pol 239	-----									
Pol 251	EAIHQVNSDIDGTWQMDCTHIEGKIVIVAIVHASGFI EAEVLPQETGRQFTALFLKLLAGRMPITHLHTDNGANFASQEVKAVAWMAGIEH	820	830	840	850	860	870	880	890	900
Pol 239	-----A-----I-----									
Pol 251	TFGVPPYNPQSQGVVEAMNHHKKNQIDRIRREQANSVETIVLMAVHCMMFRRGGIGDMTTPARLLINMITTEQEIQFQSQSKNSKFKNFRVYY	910	920	930	940	950	960	970	980	990
Pol 239	-----									
Pol 251	REGRDQLWKGEGELLWKGEGAVILKVGTDIKVPPRRKAKIKDYGGGKEVDSSSHMEDTGEAREVA	1000	1010	1020	1030	1040	1050			
Pol 239	-----									

Figure 1b. Pol CTL Epitopes

IV-10  
DEC 98

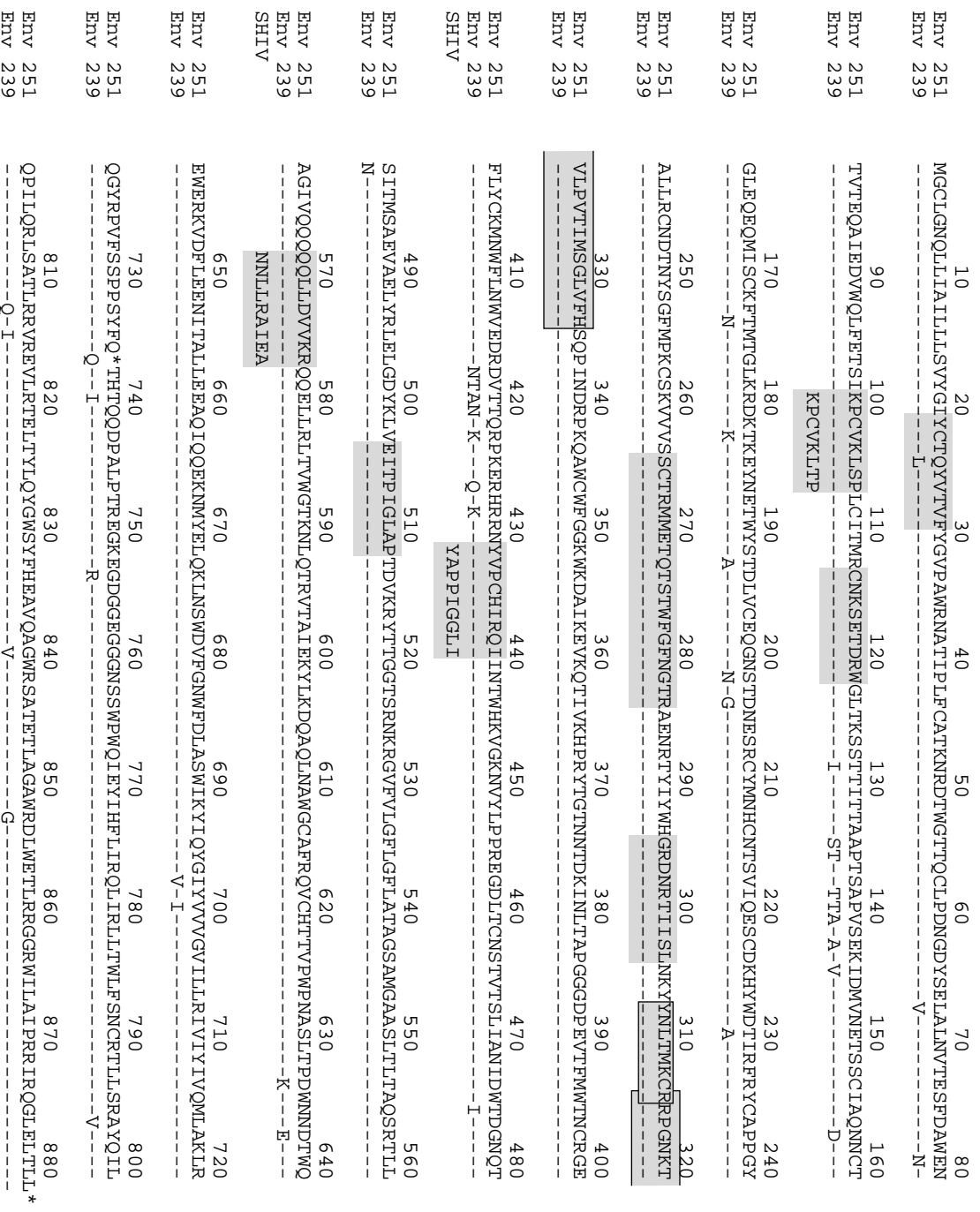


Figure 1c. Env CTL Epitopes

**SIV and SHIV Epitopes**

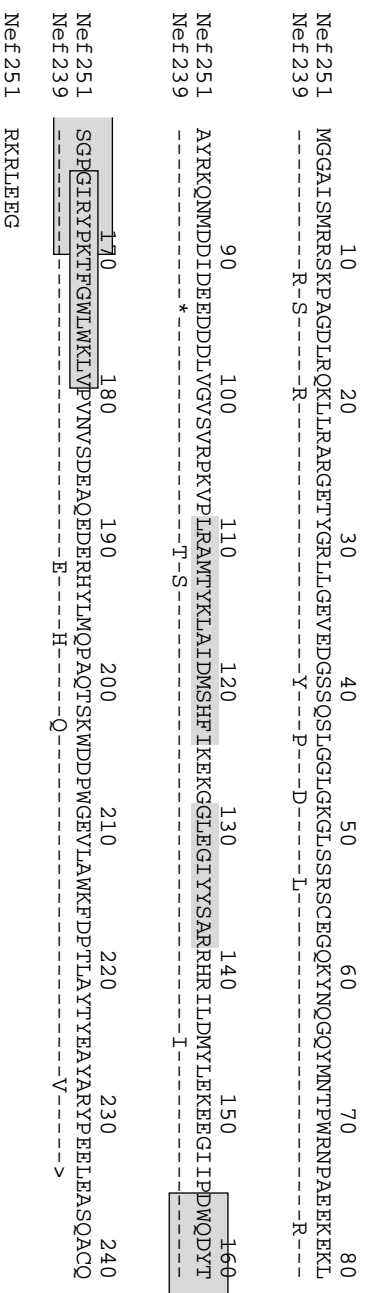


Figure 1d. Nef CTL Epitopes

## REFERENCES

- [1] Allen, T. M., J. Sidney, M. F. Delguercio, R. L. Glickman, G. L. Lensmeyer, D. A. Wiebe, R. Demars, C. D. Pauza, R. P. Johnson, A. Sette, and D. I. Watkins. 1998. Characterization of the Peptide Binding Motif of a Rhesus MHC Class I Molecule (Mamu-A\*01) That Binds an Immunodominant CTL Epitope from Simian Immunodeficiency Virus. *Journal of Immunology* **160**:6062–6071.
- [2] Bourgault, I., A. Venet, and J. P. Levy. 1992. Three epitopic peptides of the simian immunodeficiency virus Nef protein recognized by macaque cytolytic T lymphocytes. *Journal of Virology* **66**:750–6.
- [3] Egan, M. A., M. J. Kuroda, G. Voss, J. E. Schmitz, W. A. Charini, C. I. Lord, M. A. Forman, and N. L. Letvin. 1999. Use of MHC Class I/peptide Tetramers to Quantitate CD8+ CTL Specific for Dominant and Non-dominant Viral Epitopes in Simian-Human Immunodeficiency Virus-infected Rhesus Monkeys. Submitted.
- [4] Erickson, A. L., and C. M. Walker. 1994. An epitope in the V1 domain of the simian immunodeficiency virus (SIV) gp120 protein is recognized by CD8+ cytotoxic T lymphocytes from an SIV-infected rhesus macaque. *Journal of Virology* **68**:2756–9.
- [5] Geretti, A. M., E. G. Hultskote, M. E. Dings, C. A. van Baalen, G. van Amerongen, and A. D. Osterhaus. 1997. CD8+ cytotoxic T lymphocytes of a cynomolgus macaque infected with simian immunodeficiency virus (SIV) mac32H-J5 recognize a nine amino acid epitope in SIV Gag p26. *Journal of General Virology* **78**:821–4.
- [6] Gotch, F., D. Nixon, A. Gallimore, S. McAdam, and A. McMichael. 1993. Cytotoxic T lymphocyte epitopes shared between HIV-1, HIV-2, and SIV. *Journal of Medical Primatology* **22**:119–23.
- [7] Miller, M. D., H. Yamamoto, A. L. Hughes, D. I. Watkins, and N. L. Letvin. 1991. Definition of an epitope and MHC class I molecule recognized by gag-specific cytotoxic T lymphocytes in SIVmac-infected rhesus monkeys. *Journal of Immunology* **147**:320–9.
- [8] Mortara, L., F. Letourneur, H. Gras-Masse, A. Venet, J. G. Guillet, and I. Bourgault-Villada. 1998. Selection of virus variants and emergence of virus escape mutants after immunization with an epitope vaccine. *Journal of Virology* **72**:1403–10.
- [9] Voss, G., and N. L. Letvin. 1996. Definition of human immunodeficiency virus type 1 gp120 and gp41 cytotoxic T-lymphocyte epitopes and their restricting major histocompatibility complex class I alleles in simian-human immunodeficiency virus-infected rhesus monkeys. *Journal of Virology* **70**:7335–40.
- [10] Watanabe, N., S. N. McAdam, J. E. Boyson, M. S. Piekarczyk, Y. Yasutomi, D. I. Watkins, and N. L. Letvin. 1994. A simian immunodeficiency virus envelope V3 cytotoxic T-lymphocyte epitope in rhesus monkeys and its restricting major histocompatibility complex class I molecule Mamu-A\*02. *Journal of Virology* **68**:6690–6.
- [11] Yasutomi, Y., S. N. McAdam, J. E. Boyson, M. S. Piekarczyk, D. I. Watkins, and N. L. Letvin. 1995. A MHC class I B locus allele-restricted simian immunodeficiency virus envelope CTL epitope in rhesus monkeys. *Journal of Immunology* **154**:2516–22.