I-B

Beyond *Mamu-A*01+* Indian Rhesus Macaques: Continued Discovery of New MHC Class I Molecules that Bind Epitopes from the Simian AIDS Viruses

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I-B-1 Introduction

Developing an effective vaccine against HIV is a global public health priority. Nonhuman primate research will play a critical role in such development as simian immunodeficiency virus (SIV) infection of nonhuman primates is the best animal model available for AIDS, and nonhuman primates are used for testing of vaccination strategies. In the past decade, substantial progress has been made in defining and characterizing T cell responses for this animal model.

Accumulating evidence suggests that cellular immune responses play a major role in controlling HIV and SIV replication, directing recent efforts to vaccine regimens that elicit CD8+ T lymphocyte responses [McMichael & Rowland-Jones, 2001]. A variety of studies have shown associations between certain MHC class I alleles in both slow and rapid HIV/SIV disease progression [Carrington & O'Brien, 2003; Bontrop & Watkins, 2005]. Of particular interest are "elite controllers" (ECs), rare individuals who spontaneously control HIV/SIV viremia to very low levels (<50 vRNA copies/ml of plasma for HIV-infected humans [Pereyra *et al.*, 2007], <1,000 vRNA copies/ml of plasma for SIV-infected macaques [Yant *et al.*, 2006; Loffredo *et al.*, 2007b]). Understanding this natural control may aid in the development of an effective HIV vaccine.

There are, unfortunately, many difficulties inherent to studying HIV-infected humans. Viral control appears to be mediated during resolution of acute phase viremia, with the appearance of CD8+ T cell responses in both HIV-infected humans and SIV-infected macaques [Borrow *et al.*, 1994; Koup *et al.*, 1994; Reimann *et al.*, 1994; Yasutomi *et al.*, 1993; Kuroda *et al.*, 1999]. HIV is rarely diagnosed during acute infection however [Weintrob *et al.*, 2003; Kuo *et al.*, 2005; Mayben *et al.*, 2007], making the study of immune responses involved in initial control of HIV replication extremely difficult. This is further complicated by the diversity of HIV isolates with which individuals might be infected.

AIDS research with nonhuman primates provides an animal model to complement human studies. Nonhuman primates can provide examples of successful immune containment of pathogenic immunodeficiency virus replication, and researchers have direct control over key variables such as virus strain, host genotype, and route of infection. Perhaps most importantly, the immunology and pathogenesis of acute infection can easily be studied in macaques. Overall, studying immune responses to SIV in macaques is simpler than studying immune responses to HIV in humans. All macaques can be infected with a known, often clonal, viral stock. Infection with a defined viral stock enables complete and accurate immunological tracking of early immune responses by the use of corresponding peptides in *ex vivo* immunological assays. Moreover, the timing of immune responses after infection, the associated viral sequence evolution, and plasma virus concentrations may be closely monitored.

Most published studies of CD8+ T cell responses in Indian rhesus macaques have used animals which express the common MHC class I allele *Mamu-A*01*. This allele was found to be associated with lower set-point viremia in vaccinated and non-vaccinated macaques in several studies [Mao *et al.*, 2005; Mühl *et al.*, 2002; Pal *et al.*, 2002; Zhang *et al.*, 2002]. Such animals have been used largely because their CD8+ T cell responses were the first to be exhaustively identified, and *Mamu-A*01* can be readily identified using sequence-specific PCR primers [Knapp *et al.*, 1997]. The Mamu-A*01 peptide binding motif has been defined, and a comprehensive scan of the SIVmac239

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proteome yielded fourteen epitopes restricted by this MHC class I molecule [Allen *et al.*, 1998, 2001]. Tetramers are available for several of these epitopes, facilitating detailed vaccine and pathogenesis studies [Kuroda *et al.*, 1998; Allen *et al.*, 2001; Mothé *et al.*, 2002a; Egan *et al.*, 1999; Allen *et al.*, 2000].

As described in the previous compendium update and elsewhere, this focus on *Mamu-A*01*+ macaques has created a bottleneck in AIDS vaccine research due to a shortage of animals expressing this allele [O'Connor *et al.*, 2002b; Cohen, 2000]. Compared to the human system, only a small fraction of macaque MHC class I alleles have been characterized at this time [Bontrop & Watkins, 2005]. Since the publication of the last SIV compendium review in 2001 [O'Connor *et al.*, 2002b], significant advances have been made in understanding nonhuman primate immunogenetics. Two MHC class I alleles, *Mamu-B*17* and *Mamu-B*08*, were found to be enriched in EC cohorts and associated with reduced SIV replication in the chronic phase of infection [Yant *et al.*, 2006; Loffredo *et al.*, 2007b]. The binding motifs of four additional Indian rhesus macaque MHC class I alleles have been defined, and the SIVmac239 epitopes presented by these alleles identified [Mothé *et al.*, 2002b; Loffredo *et al.*, 2004; Sette *et al.*, 2005; Loffredo *et al.*, 2005]. Knowledge of the minimal-optimal epitopes restricted by these alleles should allow the use of many more Indian rhesus macaques in studies of CD8+ T cell dynamics following SIV infection, as well as a fuller understanding of the immune responses generated against SIV. Additionally, several other species of macaques are now being used in AIDS research, and their cellular immune responses are beginning to be defined.

This review highlights recent advances in AIDS research using nonhuman primate models and provides a comprehensive list of the published MHC class I and class II epitopes (Table I-B-1 and Table I-B-2). A summary of the peptide-binding motifs of several macaque MHC alleles is also presented (Table I-B-3).

I-B-2 Indian rhesus macaques: MHC class I molecules and CD8+ T cell epitopes

The Indian rhesus macaque (*Macaca mulatta*) remains the best characterized and most commonly studied nonhuman primate AIDS model. At this time, the peptide binding motifs of five MHC class I molecules (Mamu-A*01, -A*02, -A*11, -B*01, and -B*17) have been fully defined in the SIV-infected rhesus macaque model (Table I-B-3), enabling the identification of 43 of the 66 known SIV-specific CD8+ T cell epitopes (Table I-B-1) [Allen *et al.*, 1998, 2001; Mothé *et al.*, 2002b; Loffredo *et al.*, 2004; Sette *et al.*, 2005; Loffredo *et al.*, 2005]. As described above, Mamu-A*01 has been intensely investigated, as it was the first MHC class I molecule studied in detail [Allen *et al.*, 1998; Furchner *et al.*, 1999; Allen *et al.*, 2001, 2000; Egan *et al.*, 1999; Barouch *et al.*, 2002; Mothé *et al.*, 2002a; O'Connor *et al.*, 2002a; Zhang *et al.*, 2002; Pal *et al.*, 2002; Mühl *et al.*, 2002; O'Connor *et al.*, 2004; Friedrich *et al.*, 2004b; Knapp *et al.*, 1997; Peyerl *et al.*, 2003; Kuroda *et al.*, 1998; Loffredo *et al.*, 2007a]. The addition of four well-characterized MHC class I molecules significantly broadens the repertoire of immune responses that researchers may effectively monitor in animal studies. Mamu-A*02 and Mamu-B*17 are particularly helpful with twenty [Vogel *et al.*, 2002a; Loffredo *et al.*, 2004; Robinson *et al.*, 2001; Watanabe *et al.*, 1994] and twelve [Evans *et al.*, 1999, 2000; Dzuris *et al.*, 2000; Mothé *et al.*, 2002b; Horton *et al.*, 2001] epitopes, respectively, known to be restricted by these two alleles. In addition, each is present at a high frequency (>10%), in most captive rhesus macaque colonies [Kaizu *et al.*, 2007].

*Mamu-B*01*, another high frequency allele, is unusual in that it does not appear to be involved in the immune response directed against SIVmac239 [Loffredo *et al.*, 2005], although previous published reports had described six Mamu-B*01-restricted CD8+ T cell epitopes [Yasutomi *et al.*, 1995; Su *et al.*, 2005]. However, the MHC restriction of these six putative Mamu-B*01-restricted epitopes was not verified with MHC class I transfection of 721.221 cells [Yasutomi *et al.*, 1995; Su *et al.*, 2005]. In a subsequent study, it was found that the putative epitopes did not bind to Mamu-B*01 with biologically relevant affinities [Loffredo *et al.*, 2005], nor were CD8+ responses to these peptides detected in eight *Mamu-B*01*+ SIV-infected Indian rhesus macaques. Hence, vaccine immunogenicity studies in *Mamu-B*01*+ macaques may not yield useful results.

I-B-3 Indian rhesus macaques: web-based immunogenetics resources

Based on the identified SIV-specific CD8+ T cell epitopes and the peptide binding profiles of their corresponding Indian rhesus macaque MHC class I alleles, a computational algorithm was developed to predict the peptide binding and potential T cell epitopes restricted by the MHC class I molecules Mamu-A*01, -A*02, -A*11, -B*01, and -B*17 [Peters *et al.*, 2005a]. This can be accessed at the website `http://www.mamu.liai.org/`. Previous studies defined detailed peptide binding motifs, aiding discovery of the majority of identified SIVmac239 epitopes [Allen *et al.*, 1998, 2001; Mothé *et al.*, 2002b; Loffredo *et al.*, 2004; Sette *et al.*, 2005; Loffredo *et al.*, 2005]. However, it is possible that epitope screens done in chronically infected macaques failed to detect some subdominant responses restricted by these alleles. Identification and characterization

of additional subdominant responses may be aided by using the website's search engine to find the predictive binding values of peptides within regions of novel responses of unknown restriction. In addition, this resource may be of use to researchers studying other viral pathogens in the Indian rhesus macaque, expediting CD8+ T cell epitope identification. The Immune Epitope Database and Analysis Resource (IEDB) [Peters *et al.*, 2005b], located at `http://www.immuneepitope.org/`, is another useful resource recently made available. The IEDB project is hosted at the La Jolla Institute for Allergy and Immunology (LIAI), and one of its foci is the compilation of known immune (antibody and T cell) epitopes and MHC binding data. These two resources provide useful information regarding the epitopes and alleles discussed in this review, in addition to covering humans, rodents, and various other animal species.

I-B-4 Indian rhesus macaques: viral evolution and epitope cross-reactivity

As more epitopes restricted by different Indian rhesus macaque alleles have been identified and followed over the course of SIV infection, sequencing of viral RNA has revealed selection of variation by CD8+ T cells. Escape mutations are detected in many epitopes targeted by CD8+ T cells, and variation is found in epitopes restricted by each of the alleles discussed previously in the review [Evans *et al.*, 1999; Allen *et al.*, 2000; O'Connor *et al.*, 2002a, 2004; Barouch *et al.*, 2002, 2003; Peyerl *et al.*, 2003; Friedrich *et al.*, 2004b; Loffredo *et al.*, 2004; Vogel *et al.*, 2002a]. This variation is selected for with varying kinetics following infection, though for a given epitope the same escape mutation is often found in multiple animals. Recent studies have also shown that viral escape from CD8+ T cell pressures can exact a fitness cost to the virus via fitness assays and reversion experiments [Friedrich *et al.*, 2004a; Peyerl *et al.*, 2003; Friedrich *et al.*, 2004b; Barouch *et al.*, 2005].

Reactivity to escape variant peptides is frequently detectable in enzyme-linked immunospot or intracellular cytokine staining assays. However, this putative "cross-reactivity" may be an artifact of the non-physiological antigen presentation that occurs when high concentrations of exogenous antigen are used to stimulate T cells. For at least two SIVmac239 epitopes, Mamu-A*01-restricted $Gag_{181\text{-}189}$CM9 and $Tat_{28\text{-}35}$SL8, consistent reactivity to escape variant peptides has been observed, albeit with reduced functional avidity. By contrast, cells infected with corresponding escape variant viruses were not recognized by CD8+ T cell lines specific for the wild-type epitope [Loffredo *et al.*, 2007a; Valentine *et al.*, 2007]. Whether *de novo* responses specific for escape variant sequences are generated has not been rigorously studied.

I-B-5 Indian rhesus macaques: natural containment of pathogenic SIV replication

The most interesting, recent studies of Indian rhesus macaque immunogenetics involved the characterization of two MHC class I alleles associated with slow disease progression in SIV-infected macaques. Both *Mamu-B*17* and *Mamu-B*08*, unlike *Mamu-A*01*, are MHC class I alleles significantly enriched in elite controller (EC) cohorts [Yant *et al.*, 2006; Loffredo *et al.*, 2007b]. Fourteen of the sixteen (88%) EC macaques identified from a cohort of 196 SIVmac239-infected macaques expressed either *Mamu-B*17* or *Mamu-B*08*. This percentage is similar to a previous study that demonstrated the overrepresentation of *HLA-B*5701* (11 of 13, 85%) in a cohort of long term nonprogressors / ECs with normal CD4+ T cells counts and HIV replication less than 50 vRNA copies/ml [Migueles *et al.*, 2000]. *Mamu-B*17*+ and *Mamu-B*08*+ macaques also exhibit a greater reduction in SIV viremia compared to *Mamu-A*01*+ macaques in a cohort of 196 SIVmac239-infected macaques [Yant *et al.*, 2006; Loffredo *et al.*, 2007b].

Intriguingly, the peptide binding motif of Mamu-B*17 is broadly similar to that of HLA-B57, while the Mamu-B*08 motif resembles that of HLA-B27. *HLA-B57* and *-B27* are associated with lower plasma virus concentrations in HIV-infected individuals [Carrington & O'Brien, 2003]. Although Mamu-B*17 seems to tolerate a wider array of residues at position two than HLA-B57, both molecules require `W`, `F`, or `Y` at the C-terminal anchor position [Mothé *et al.*, 2002b; Rammensee *et al.*, 1999; Marsh *et al.*, 2000]. A previous study demonstrated that another macaque MHC class I molecule, Mamu-B*03, binds peptides conforming to the HLA-B27 binding motif [Dzuris *et al.*, 2000]. This allele was also associated with slow SIV disease progression [Evans *et al.*, 1999], but additional studies were hindered by the low frequency of this allele in captive rhesus macaques (overall < 1%; Kaizu *et al.* [2007]). Mamu-B*03 and Mamu-B*08 are almost identical in amino acid sequence [Boyson *et al.*, 1996], with only two amino acid differences between Mamu-B*03 and Mamu-B*08 in regions that influence peptide binding and antigen recognition [Bjorkman *et al.*, 1987; Garrett *et al.*, 1989]. Both differences reside in the alpha-1 domain (exon two). Therefore, it is likely that Mamu-B*08 also shares this HLA-B27 binding profile. This hypothesis is supported by the fact that all seven Mamu-B*08-restricted CD8+ T cell epitopes currently described (Table I-B-1) fit the peptide-binding motif for HLA-B27 of an `R` at position two and an `L` at the C-terminus [Loffredo *et al.*, 2007c]. Studies to completely define the Mamu-B*08 peptide bind-

ing motif are ongoing, and should help to identify the complete repertoire of SIVmac239-specific CD8+ T cell epitopes restricted by Mamu-B*08.

The discovery of Mamu-B*17 and Mamu-B*08 now provide us with a unique opportunity not previously available due to technological and assay limitations. Currently, we have found that about 20–25% of *Mamu-B*17*+ and about 50% of *Mamu-B*08*+ SIV-infected Indian rhesus macaques are elite controllers [Yant *et al.*, 2006; Loffredo *et al.*, 2007b]. With peptide binding motifs similar to the analogous human EC alleles *HLA-B57* and *HLA-B27*, respectively, and definition of at least seven SIV epitopes for each macaque allele (Table I-B-1), investigators now have the resources to study successful immune responses against AIDS viruses in the SIV-infected macaque model.

I-B-6 Indian rhesus macaques: MHC class II molecules and CD4+ T cell epitopes

As with HIV, mapping of CD4+ T cell epitopes in SIV has lagged behind studies of CD8+ T cell epitopes. This is due in part to the difficulty in maintaining such responses in the face of ongoing viral replication, as HIV-specific CD4+ T cells are preferentially infected [Douek *et al.*, 2002]. Initially, studies focused on identifying Env-specific CD4+ T cell responses in SHIV-infected macaques [Lekutis & Letvin, 1997; Dzuris *et al.*, 2001; Lekutis *et al.*, 1997]. Two MHC class II molecules, Mamu-DRB1*0406 and Mamu-DRB*w201, presented three Env-specific CD4+ T cell responses, enabling an Env-specific MHC class II tetramer to be constructed [Kuroda *et al.*, 2000]. Later, peptide binding motifs for these two alleles were generated, and used to identify other SIV-derived peptides that Mamu-DRB1*0406 and Mamu-DRB*w201 might present [Dzuris *et al.*, 2001]. This investigation also discussed two new novel CD4+ T cell responses against Gag and Rev that were restricted by Mamu-DRB*w201. Unpublished data from Giraldo Vela *et al.* describe five additional MHC class II alleles that restrict CD4+ T cell responses in Gag, Rev, Nef, and Vpx, thereby doubling the number of known SIV/SHIV epitopes (Table I-B-2). Numerous other regions of SIV have been documented to contain CD4+ T cell epitopes [Mills *et al.*, 1991; Sarkar *et al.*, 2002; Vogel *et al.*, 2002b]. However, the MHC class II restriction of the majority of these responses remains undefined.

I-B-7 Alternatives to the SIV-infected Indian rhesus macaque animal model

The demand for Indian rhesus macaques has lessened somewhat with a growing interest in alternative nonhuman primate models for AIDS. Currently, pigtail macaques (*Macaca nemestrina*) are being used in epitope identification and vaccine/pathogenesis studies. In addition, vaccine-induced immune responses have been effective at controlling SIVmac239 replication in Burmese macaques (*Macaca mulatta*), while the simple MHC genetics of Mauritian cynomolgus macaques (*Macaca fascicularis*) may offer unique opportunities for future SIV studies. There are, however, some key differences between these groups of animals, which are pertinent to SIV research.

All of these macaques, of the genus *Macaca*, are native to Asia and are non-natural hosts for SIV. Burmese-origin rhesus macaques, while the same species as Indian-origin rhesus macaques, are from a geographically separate population and possess divergent MHC class I alleles. Different subpopulations of rhesus macaques (Indian, Burmese, and Chinese origin) can be readily distinguished by mitochondrial DNA sequencing [Smith & McDonough, 2005], and by single nucleotide polymorphism analysis [Ferguson *et al.*, 2007; Malhi *et al.*, 2007], tools that may be useful for determining ancestry of animals with unknown origin. The most recent common ancestor of the rhesus macaque species is estimated to have lived about 1.9 million years ago, around the time rhesus macaques diverged from cynomolgus macaques [Hernandez *et al.*, 2007]. Pigtailed macaques are somewhat more distantly related, having separated from the rhesus macaque lineage about 3.5 million years ago [Morales & Melnick, 1998].

These different groups of macaques experience varying degrees of pathogenicity following infection with commonly used SIV isolates. A comparative study by Reimann *et al.* [2005] found no significant difference in the acute-phase peak of viremia in SIVmac251-infected Indian rhesus, Chinese rhesus, and cynomolgus macaques, while a separate study of SIVmac251-infected pigtail macaques measured a very similar acute-phase viral peak [Batten *et al.*, 2006]. Differences in plasma virus concentrations emerge after acute infection, the timing of which suggests a determinative role for the adaptive immune response, rather than an inherent difference in the replicative capacity of SIV in these animals. Overall, rhesus macaques of Indian descent consistently have the highest viral set-points. In comparison, it appears that the chronic-phase plasma viremia of SIVmac239 in Burmese rhesus macaques (geometric mean of 65,000 vRNA copies/ml in one small study [Yamamoto *et al.*, 2007]) is similar, or perhaps slightly lower than that observed in a large cohort of Indian rhesus macaques (geometric mean 223,800 vRNA copies/ml, [Loffredo *et al.*, 2007b]). However, a direct comparison of these animals has not been published. Meanwhile, cynomolgus macaques have significantly reduced plasma virus concentrations (approximately two-logs) compared to Indian-origin rhesus macaques, with a large proportion of these cynomolgus macaques becoming ECs after SIVmac251 challenge [Reimann *et al.*, 2005].

Pigtail macaques are also productively infected with SIVmac251, with substantial variability in their viral set-point having been documented [Batten *et al.*, 2006].

Why different macaque species/subspecies have different disease courses following infection with the same virus has not been defined, but it is notable that SIV isolates used in the majority of studies (SIVmac239, SIVmac251, and SHIV-89.6P) have been passaged in rhesus macaques of Indian origin. One study has shown that passaging SIV in rhesus macaques of Chinese origin resulted in increased viral loads in subsequently infected Chinese macaques [Burdo *et al.*, 2005]. While the mutations acquired were not characterized, this study suggests that species-specific adaptations might play a role in determining viral set-point for different groups of animals.

I-B-8 Burmese rhesus macaques

Several interesting vaccine experiments have utilized SIV-infected Burmese rhesus macaques. A Gag-expressing DNA-prime/Sendai virus vector boost vaccination led to control of SIVmac239 replication in five of eight vaccinated Burmese macaques [Matano *et al.*, 2004]. By week five, the successful vaccinees had undetectable plasma virus concentrations. Interestingly, viruses from these five animals had escape mutations in Gag that appeared to have occurred at a high fitness cost to the virus [Matano *et al.*, 2004; Kobayashi *et al.*, 2005]. The escape analysis demonstrated that three vaccinees shared an MHC class I haplotype (90-120-Ia), which restricted some of the Gag-specific CD8+ T cell responses (Table I-B-1). Follow-up studies in these animals have shown that multiple Gag-specific CD8+ T lymphocyte responses were involved in the vaccine-induced control [Kawada *et al.*, 2006], and additional viral mutations associated with this MHC class I haplotype (90-120-Ia) accumulated. At this time, responses have not been mapped to specific MHC class I alleles.

Additionally, SIV-specific CD4 responses in the Burmese macaques are being investigated and appear to be associated with viral control [Lun *et al.*, 2004]. SIV-specific CD8+ T cells that are not directed against Gag also appear to be important in Burmese macaques, although responses have not yet been mapped [Kawada *et al.*, 2007].

I-B-9 Pigtail macaques

Until recently, research with pigtail macaques had been hampered by a lack of defined viral epitopes and limited characterization of pigtail macaque MHC class I alleles. However, over the past several years considerable effort has been directed toward understanding the immunogenetics of pigtail macaques, widening the resources available to researchers. Importantly, many *Macaca nemestrina* MHC class I alleles (*Mane*) have now been characterized from more than 100 pigtail macaques [Lafont *et al.*, 2003; Pratt *et al.*, 2006; Smith *et al.*, 2005a].

Immunogenetic analyses of these animals have identified several defined minimal-optimal epitopes in Gag (Table I-B-1). Of particular interest is an immunodominant response, $Gag_{164\text{-}172}$KP9, restricted by the high frequency allele, Mane-A*10 (and later Mane-A*16, an MHC class I allele of similar sequence) [Smith *et al.*, 2005a,b]. This SIV epitope $Gag_{164\text{-}172}$KP9 has been studied extensively and parallels can be drawn to the Mamu-A*01-restricted CD8+ T cell epitope $Gag_{181\text{-}189}$CM9. Viral escape at position two of this epitope leads to loss of epitope recognition [Fernandez *et al.*, 2005]. Viral fitness was also impaired by this mutation, as evidenced by sequence reversion when the selective pressure of the $Gag_{164\text{-}172}$KP9-specific immune responses was removed [Fernandez *et al.*, 2005; Loh *et al.*, 2007; Fernandez *et al.*, 2007]. In addition, unvaccinated pigtail macaques infected with SIVmac251 that directed a response against $Gag_{164\text{-}172}$KP9 have significantly reduced plasma viremia compared to $Gag_{164\text{-}172}$KP9 non-responders [Smith *et al.*, 2005a].

Additional research has also identified three subdominant Gag responses in pigtail macaques restricted by various other MHC class I alleles (Table I-B-1) [Smith *et al.*, 2005a; Fernandez *et al.*, 2005; Pratt *et al.*, 2006]. Furthermore, several other Gag-specific CD8 and CD4 responses are currently being mapped, and their restriction elements determined [Fernandez *et al.*, 2005]. Finally, another study provided a comparative virological and immunological analysis of a variety of primate lentiviruses showing the variable pathogenicity of a variety of SIV/SHIVs that are available for use in pigtail macaques [Batten *et al.*, 2006].

I-B-10 Mauritian cynomolgus macaques

Research with cynomolgus macaques has not been as common as research with rhesus macaques because many SIV and SHIV strains are less pathogenic in the cynomolgus species [Reimann *et al.*, 2005]. However, lately there has been renewed interest in studying the SIV-specific immune responses in these animals, largely due to the unique immunogenetics of cynomolgus macaques from the Indian Ocean island of Mauritius. During the definition of 66 MHC class I alleles in cynomolgus macaques of Chinese, Vietnamese, and Mauritian origin, it was discovered that most MHC class I alleles could be divided by geographic origin, with few alleles shared by animals descended from geographically distinct populations [Krebs *et al.*, 2005]. This is similar to findings in Chinese and Indian rhesus macaques, which do not express the same MHC class I alleles [Ling *et al.*, 2002; Trichel *et al.*, 2002]. These data highlight the point that macaques from different origins are not interchangeable in studies of cellular immunity.

However, also of great interest was the finding that more than 50% of Mauritian cynomolgus macaques shared a combination of three MHC class I alleles. In contrast, the most frequent Indian rhesus macaque alleles are present at a frequency of only 25-30% in any given population [Kaizu *et al.*, 2007].

Follow-up analysis using microsatellite markers revealed that the Mauritian cynomolgus macaques have extremely simple MHC genetics, with six distinct chromosomal haplotypes accounting for almost all of the MHC class I and class II diversity in this population, likely due to these animals being recently descended from a small founder population [Lawler *et al.*, 1995]. Remarkably, 39% of Mauritian cynomolgus macaques carry at least one copy of the most frequent MHC haplotype, with 8% being homozygous for this haplotype [Wiseman *et al.*, 2007]. This extensive sharing of MHC haplotypes is unprecedented among macaques [Otting *et al.*, 2005; Penedo *et al.*, 2005; Krebs *et al.*, 2005; Wiseman *et al.*, 2007] and could expand the scope of SIV studies undertaken in nonhuman primates by allowing greater control over genetic variability. Studies are now possible in which entire MHC class I haplotypes are matched, rather than a single MHC class I molecule, as is typical in Indian rhesus macaques studies. This may simplify studying cellular immune responses by eliminating unknown influences of unmatched MHC class I alleles. In addition, adoptive lymphocyte transfers that are possible in inbred mouse strains might now be technically feasible with MHC-identical macaques. Recently, the MHC class II alleles for the six common haplotypes were characterized in these animals, enabling researchers to generate useful molecular reagents for CD4+ T cell studies [O'Connor *et al.*, 2007].

At this point, SIV epitopes restricted by these high frequency MHC class I alleles have not been mapped in Mauritian cynomolgus macaques. However, a recent study defined a single Gag minimal-optimal epitope of unknown MHC class I restriction [Negri *et al.*, 2006]. In addition, a similar breadth of cellular immune responses in Gag, Pol, Tat, Env, Rev, and Nef was identified in two MHC class I-identical SIVmac239-infected macaques. Corresponding viral variation was seen in Tat, Rev, and Nef that may prove to be escape from CD8+ T cell pressures [Wiseman *et al.*, 2007].

I-B-11 Advances in MHC genotyping methods

To support efficient utilization of limited nonhuman primate resources and maximize the understanding of SIV-specific immune responses in vaccine and viral pathogenesis studies, accurate and efficient MHC genotyping technologies are needed.

PCR amplification with sequence specific primers (PCR-SSP) is currently the preferred method for MHC genotyping at allelic-level resolution in many human clinical laboratories [Olerup & Zetterquist, 1991, 1992] because this technique is specific, robust, and straightforward. The PCR-SSP platform enables rapid, high throughput analysis, yet it is cost effective and requires inexpensive equipment. These benefits have made it a productive choice for MHC class I genotyping of Indian rhesus macaques. Initial investigations designed PCR-SSP primers for a single MHC class I allele of interest, with unique PCR amplification conditions [Knapp *et al.*, 1997; Vogel *et al.*, 2002a; Horton *et al.*, 2001; Loffredo *et al.*, 2005; Robinson *et al.*, 2001; Schramm *et al.*, 2001; Su *et al.*, 2005]. However, recent technological improvements have allowed the use of unified PCR conditions, allowing simultaneous PCR amplification of eight Indian rhesus macaque MHC class I alleles [Kaizu *et al.*, 2007]. These alleles were selected since they have been implicated in the restriction of SIV-specific CD8+ T cell epitopes. Molecular genotyping of *Mamu-A*01*, *-A*02*, *-A*08*, *-A*11*, *-B*01*, *-B*03*, *-B*04*, and *-B*17* can now be conducted in a high throughput fashion, using genomic DNA as a template.

Although the importance of defining the complete MHC class I repertoire of a given macaque is well recognized, development of a simple, comprehensive molecular genotyping method for rhesus macaque MHC class I alleles has been difficult. During the evolution of this species, the *Mamu-A* and *Mamu-B* loci were duplicated [Bontrop & Watkins, 2005; Otting *et al.*, 2005; Daza-Vamenta *et al.*, 2004; Boyson *et al.*, 1996; Kulski *et al.*, 2004]. Therefore, macaques express a variable number of MHC class I alleles per haplotype.

The complexity of the nonhuman primate MHC is problematic for PCR-SSP-based genotyping since this technique can only detect known MHC alleles. Moreover, it is difficult to develop allele-specific primers in the absence of a reasonably complete allele database. The established methods to identify all of the alleles in a given macaque involve PCR cloning and sequencing, or generating macaque-derived cDNA libraries. While cDNA libraries are the gold standard in identifying MHC alleles, the process is very time consuming and expensive. PCR cloning and sequencing is a less time consuming alternative and requires less starting material. However, this technique may introduce PCR artifacts or provide incomplete MHC coverage due to primer mismatches. Therefore, alternative genotyping methods for rapid identification of all of the alleles in a given animal are being investigated.

The most developed of these techniques is reference strand-mediated conformational analysis, or RSCA. RSCA is a modified heteroduplex assay capable of characterizing complex gene families [Argüello & Madrigal, 1999; Argüello *et al.*, 2003; Kennedy *et al.*, 2005; Krebs *et al.*, 2005]. Heteroduplexes are created by hybridization between fluorescently labeled reference strands and individ-

ual MHC alleles. RSCA can resolve individual MHC alleles because each MHC/reference strand heteroduplex produces a characteristic and reproducible mobility profile when electrophoresed in a nondenaturing polyacrylamide gel. The mobility profile of each MHC allele can be further resolved for higher degrees of sensitivity with the addition of alternative reference strands. RSCA, unlike conventional genotyping techniques (i.e. PCR-SSP), can detect multiple known and unknown MHC alleles in a single reaction, enabling the researcher to define the full complement of expressed class I alleles in a given animal.

RSCA has been used in several nonhuman primate studies, including the SIV models summarized in this review. These applications include MHC genotyping, allele discovery, epitope restriction determination, and identifying haplotype inheritance patterns [Krebs *et al.*, 2005; Smith *et al.*, 2005a,b; Pratt *et al.*, 2006; Baquero *et al.*, 2006; Wiseman *et al.*, 2007; Tanaka-Takahashi *et al.*, 2007]. Current RSCA platforms can be easily expanded to incorporate newly discovered alleles once a mobility profile is established. However, RSCA is best utilized in tandem with other MHC genotyping techniques due to limited sensitivity in some circumstances [Pratt *et al.*, 2006; Tanaka-Takahashi *et al.*, 2007]. In addition, this technique is still technically demanding [Krebs *et al.*, 2005; Pratt *et al.*, 2006; Smith *et al.*, 2005a,b], so genotyping via capillary electrophoresis is currently being explored for higher throughput and increased sensitivity.

Another alternative for rapid MHC genotyping is microsatellite analysis, also known as short tandem repeat (STR) genotyping. For years, microsatellite genotyping has been applied for tissue matching and donor screening in human transplantation [Carrington & Wade, 1996; Foissac *et al.*, 2001]. MHC genotyping using microsatellite markers has become more common because the method is sensitive, accurate, and cost effective. With the recent publication of the genomic sequence of the entire rhesus macaque MHC [Daza-Vamenta *et al.*, 2004], and more recently the complete genome of an Indian-origin rhesus macaque [Gibbs *et al.*, 2007], additional microsatellite sites have been identified for use in nonhuman primate studies. Microsatellite maps of the macaque MHC were recently published [Wojcechowskyj *et al.*, 2007; Wiseman *et al.*, 2007] in addition to a core marker set of four multiplex PCR panels comprising fifteen autosomal STR loci for genetic managements of rhesus macaque colonies [Kanthaswamy *et al.*, 2006].

Microsatellite genotyping has already been utilized in rhesus macaque breeding groups to help define MHC haplotypes, track descent, and to differentiate chromosome configurations that would appear identical based on more limited allele-specific genotyping [Penedo *et al.*, 2005]. More recently, microsatellite analysis was instrumental in characterizing the simple genetics of Mauritian cynomolgus macaques [Wiseman *et al.*, 2007]. In order to define MHC haplotypes in these animals, a panel of eighteen microsatellite markers, spanning the entire 5-Mb MHC region was utilized. The majority of the primers used to amplify these microsatellite markers were adapted from rhesus genomic sequences [Daza-Vamenta *et al.*, 2004; Gourraud *et al.*, 2004; Penedo *et al.*, 2005]. In a cohort of more than 100 feral Mauritian cynomolgus macaques, this analysis was applied to identify the six common haplotypes that account for two-thirds of the MHC haplotypes in these animals, as described above [Wiseman *et al.*, 2007]. Microsatellite genotyping can also be used for direct genotyping for a specific MHC class allele if a tightly linked microsatellite marker is identified. For example, the H11-9268 microsatellite marker has shown exceptional linkage to *Mamu-B*17* in a cohort of 75 Indian rhesus macaques [Wojcechowskyj *et al.*, 2007]. In the future, this technology may assist in selective breeding of nonhuman primates by identifying homozygous animals, something that is not possible with current PCR-SSP strategies.

Identification of single nucleotide polymorphisms (SNPs) has also been aided by the completion of the rhesus macaque genome. Recently, 23,000 candidate SNPs were identified throughout the rhesus macaque genome and compiled into a web resource called *Mamu*SNP that is housed at `http://mamusnp.ucdavis.edu` [Malhi *et al.*, 2007]. Two other studies identified and applied SNPs to population genetic analyses between Indian-origin and Chinese-origin rhesus macaques to understand the demographic history and genetic divergence of these two groups [Ferguson *et al.*, 2007; Hernandez *et al.*, 2007]. Like microsatellite analysis, genetic studies using SNPs will play an important role in establishing ancestry, directing macaque breeding programs, and helping to map and identify genes involved in complex diseases in the future.

I-B-12 Concluding remarks

Nonhuman primate AIDS research is critical to HIV vaccine development and pathogenesis studies. A great deal of progress has been made in improving the nonhuman primate model in the last decade. The cellular immune responses of Indian rhesus macaques are far better defined, and additional macaque models, Burmese rhesus, pigtail, and cynomolgus, which are useful for AIDS research have been identified. However, despite this progress, our understanding of macaque immunogenetics is still is rudimentary. Much work remains to be done in identifying MHC class I and class II alleles in these macaques, in mapping immune responses, and in characterizing which responses are effective against immunodeficiency viruses. Understanding these basic issues may then facilitate pathogenesis studies, and the rational design and testing of T cell-based vaccination strategies.

I-B-13 Table of SIV epitopes

Table I-B-1: Known MHC class I epitopes and restricting molecules

Virus	Species[a]	Protein	Amino acid positions[b]	Short name	Sequence	Restricting molecule[c]	GenBank Acc. No.[d]	Reference
SIVmac239	Rhesus	Gag	149-157	LW9	LSPRTLNAW	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239, SIVsmE660, SIVsmH4	Rhesus	Gag	181-189	CM9	CTPYDINQM	Mamu-A*01[e]	U50836	Allen *et al.*, 2001, 1998; Furchner *et al.*, 1999
SIVmac239	Rhesus	Gag	254-262	QI9	QNPIPVGNI	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Gag	372-379	LF8	LAPVPIPF	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Pol	147-156	LV10	LGPHYTPKIV	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Pol	592-600	QV9	QVPKFHLPV	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239, SIVmac251, SHIV-89.6, SHIV-HXBc2	Rhesus	Pol	625-633	SV9	STPPLVRLV	Mamu-A*01[e]	U50836	Allen *et al.*, 2001; Egan *et al.*, 1999
SIVmac251	Rhesus	Pol	692-700	SV9	SGPK**T**NIIV[f]	Mamu-A*01[e]	U50836	Allen *et al.*, 2001; O'Connor *et al.*, 2004
SIVmac239	Rhesus	Pol	696-704	SV9	SGPK**A**NIIV[f]	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Env	233-240	CL8	CAPPGYAL	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239, SIVsmE660, (SIVsmH4)	Rhesus	Env	233-241 (234-242)	CL9	CAPPGYALL	Mamu-A*01[e]	U50836	Allen *et al.*, 2001; Furchner *et al.*, 1999
SHIV-89.6, SHIV-HXBc2	Rhesus	Env	397-405	YI9	YAPPISGQI	Mamu-A*01[e]	U50836	Egan *et al.*, 1999
SIVmac239	Rhesus	Env	620-628	TL9	TVPWPN**AS**L[g]	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVsmH4, SIVsmE660	Rhesus	Env	626-634	TL9	TVPWPN**ET**L[g]	Mamu-A*01[e]	U50836	Furchner *et al.*, 1999
SIVmac239	Rhesus	Env	726-735	ST10	SSPPSYFQQT	Mamu-A*01[e]	U50836	Allen *et al.*, 2001; O'Connor *et al.*, 2004
SIVmac251	Rhesus	Env	729-738	ST10	SPPSYFQTHT	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Tat	28-35	SL8	**S**TPESANL[h]	Mamu-A*01[e]	U50836	Allen *et al.*, 2001, 2000
SIVmac251	Rhesus	Tat	28-35	TL8	**T**TPESANL[h]	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Vif	144-152	QA9	QVPSLQYLA	Mamu-A*01[e]	U50836	Allen *et al.*, 2001
SIVmac239	Rhesus	Vpx	8-18	II11	IPPGNSGEETI	Mamu-A*01[e]	U50836	Allen *et al.*, 2001

Table I-B-1: Known MHC class I epitopes and restricting molecules (cont.)

Virus	Species[a]	Protein	Amino acid positions[b]	Short name	Sequence	Restricting molecule[c]	GenBank Acc. No.[d]	Reference
SIVmac239	Rhesus	Gag	71-79	GY9	GSENLKSLY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004; Vogel *et al.*, 2002a
SIVmac239	Rhesus	Pol	324-332	FF9	FSIPLDEEF	Mamu-A*02[i,j]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Pol	518-526	LY9	LSQEQEGCY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Env	296-304	RY9	RTIISLNKY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac251	Rhesus	Env	306-313	YR8	YNLTMKCR	Mamu-A*02[i]	U50837	Watanabe *et al.*, 1994
SIVmac239	Rhesus	Env	317-325	KM9	KTVLPVTIM	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Env	359-367	QY9	QTIVKHPRY	Mamu-A*02[i,j]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Env	519-528	GF10	GTSRNKRGVF	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Env	760-768	SY9	SSWPWQIEY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Env	788-795	RY8	RTLLSRVY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Nef	20-28	LY9	LLRARGETY	Mamu-A*02[i,j]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Nef	110-119	TM10	TMSYKLAIDM	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239, SIVmac251, SHIV-89.6(P)	Rhesus	Nef	159-167	YY9	YTSGPGIRY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004; Robinson *et al.*, 2001; Vogel *et al.*, 2002a
SIVmac239	Rhesus	Nef	169-177	KL9	KTFGWLWKL	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Nef	221-229	YY9	YTYEAYVRY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Nef	248-256	LM9	LTARGLLNM	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Vif	89-97	IW9	ITWYSKNFW	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Vif	97-104	WY8	WTDVTPNY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Vif	104-113	YY10	YADILLHSTY	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Vpr	63-71	RM9	RILQRALFM	Mamu-A*02[i]	U50837	Loffredo *et al.*, 2004
SIVmac239	Rhesus	Pol	782-789	YL8	YHSNVKEL	Mamu-A*07	AF161324	Sacha *et al.*, 2007
SHIV-HXBc2	Rhesus	Env	117-124	KP8	KPCVKLTP	Mamu-A*08	AF243179	Voss & Letvin, 1996
SIVmac239	Rhesus	Gag	178-186	SI9	SEGCTPYDI	Mamu-A*11	AF199357	Sette *et al.*, 2005
SIVmac239	Rhesus	Pol	92-100	AL9	AERKQREAL	Mamu-A*11	AF199357	Sette *et al.*, 2005
SIVmac239	Rhesus	Pol	507-517	AI11	AEAEYEENKII	Mamu-A*11	AF199357	Sette *et al.*, 2005
SIVmac239, (SIVppm)	Rhesus	Env	495-502 (497-504)	GI8	GDYKLVEI	Mamu-A*11	AF199357	Dzuris *et al.*, 2000; Evans *et al.*, 2000, 1999; Sette *et al.*, 2005
SIVmac239	Rhesus	Nef	124-132	KI9	KEKGGLEGI	Mamu-A*11	AF199357	Sette *et al.*, 2005
SIVmac239	Rhesus	Vpr	13-21	RV9	REPWDEWVV	Mamu-A*11	AF199357	Sette *et al.*, 2005

Table I-B-1: Known MHC class I epitopes and restricting molecules (cont.)

Virus	Species[a]	Protein	Amino acid positions[b]	Short name	Sequence	Restricting molecule[c]	GenBank Acc. No.[d]	Reference
SIVppm	Rhesus	Env	575-583	KL9	KRQQELLRL	Mamu-B*03	U41825	Evans *et al.*, 1999, 2000
SIVppm	Rhesus	Nef	136-146	AL11	ARRHRILD**I**YL[k]	Mamu-B*03	U41825	Dzuris *et al.*, 2000; Evans *et al.*, 2000, 1999
SIVppm	Rhesus	Nef	136-146	AL11	ARRHRILD**M**YL[k]	Mamu-B*03	U41825	Dzuris *et al.*, 2000; Evans *et al.*, 2000, 1999
SIVppm	Rhesus	Nef	62-69 (62-70)	QP8 (QW9)	QGQYMNTP(W)	Mamu-B*04	U41826	Dzuris *et al.*, 2000; Evans *et al.*, 2000, 1999
SIVmac239	Rhesus	Rev	12-20	KL9	KRLRLIHLL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SIVmac239	Rhesus	Rev	44-51	RL8	RRRWQQLL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SIVmac239	Rhesus	Nef	8-16	RL9	RRSRPSGDL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SIVmac239	Rhesus	Nef	137-146	RL10	RRHRILDIYL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SIVmac239	Rhesus	Nef	246-254	RL9	RRLTARGLL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SIVmac239	Rhesus	Vif	123-131	RL9	RRAIRGEQL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SIVmac239	Rhesus	Vif	172-179	RL8	RRDNRRGL	Mamu-B*08	U41830	Loffredo *et al.*, 2007c
SHIV-HXBc2	Rhesus	Env	553-561	NA9	NNLLRAIEA	Mamu-B*12	AF243178	Voss & Letvin, 1996
SIVmac239	Rhesus	Pol	372-379	MF8	MRHVLEPF	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Pol	435-443	FW9	FQWMGYELW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Pol	604-613	VW10	VWEQWWTDYW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Env	241-251	LF11	LRCNDTNYSGF	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Env	816-825	LY10	LRTELTYLQY	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Env	830-838	FW9	FHEAVQAVW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Nef	165-173	IW9	IR**Y**PKTFGW[l]	Mamu-B*17	AF199358	Horton *et al.*, 2001; Mothé *et al.*, 2002b
SIVppm	Rhesus	Nef	165-173	IW9	IR**F**PKTFGW[l]	Mamu-B*17	AF199358	Dzuris *et al.*, 2000; Evans *et al.*, 2000, 1999
SIVmac239	Rhesus	Nef	195-203	MW9	MHPAQTSQW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Nef	199-207	QW9	QTSQWDDPW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Vif	44-52	HW9	HFKVGWAWW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Vif	66-73	HW8	HLEVQGYW	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Rhesus	Vif	135-143	CY9	CRFPRAHKY	Mamu-B*17	AF199358	Mothé *et al.*, 2002b
SIVmac239	Burmese rhesus	Gag	206-216	IL11	IINEEAADWDL	90-120-Ia (haplotype)[m]		Matano *et al.*, 2004
SIVmac239	Burmese rhesus	Gag	241-249	SW9	SSVDEQIQW	90-120-Ia (haplotype)[m]		Kawada *et al.*, 2006; Matano *et al.*, 2004

Table I-B-1: Known MHC class I epitopes and restricting molecules (cont.)

Virus	Species[a]	Protein	Amino acid positions[b]	Short name	Sequence	Restricting molecule[c]	GenBank Acc. No.[d]	Reference
SIVmac239	Burmese rhesus	Gag	373-380	AA8	APVPIPFA	90-120-Ia (haplotype)[m]		Kawada *et al.*, 2006; Matano *et al.*, 2004
SIVmac239, SIVmac251, SHIVmn229, SHIV-SF162P3	Pigtail	Gag	164-172	KP9	KKFGAEVVP	Mane-A*10[n] Mane-A*16	AY557348 AY557354	Fernandez *et al.*, 2005; Smith *et al.*, 2005a,b
SIVmac239, SHIVmn229, SHIV-SF162P3	Pigtail	Gag	251-258	YP8	YRQQNPIP	Mane-A*11 Mane-A*12	AY557349 AY557350	Fernandez *et al.*, 2005; Smith *et al.*, 2005a
SIVmac239, SHIVmn229, SHIV-SF162P3	Pigtail	Gag	371-379	AF9	ALAPVPIPF	Mane-A*17	DQ886026	Fernandez *et al.*, 2005; Loh *et al.*, 2007; Pratt *et al.*, 2006
SIVmac239, SHIVmn229, SHIV-SF162P3	Pigtail	Gag	28-36	KW9	KYMLKHVVW	Mane-B*10	AY557355	Fernandez *et al.*, 2005; Loh *et al.*, 2007; Smith *et al.*, 2005a
SIVmac32H-J5	Cynomologus	Gag	242-250	SM9	SVDEQIQWM	Mafa-A*02	AB154761	Geretti *et al.*, 1997

Notes:

[a] Unless specified, rhesus designation implies rhesus macaques of Indian descent.

[b] Positions indicated for SIVmac239 or first virus listed for each epitope unless otherwise specified. Epitopes in Pol are numbered from the open reading frame.

[c] MHC class I molecule designations: rhesus macaque (*Macaca mulatta*; *Mamu*); cynomolgus macaque (*Macaca fascicularis*; *Mafa*); pigtail macaque (*Macaca nemestrina*; *Mane*).

[d] The GenBank Acc. No. listed for each MHC class I restricting allele contains the most complete nucleotide sequence for that corresponding allele. Multiple entries were marked if several full length sequences were available.

[e] The following GenBank Acc. No. are also listed for Mamu-A*01: AJ539307 and NM 001048246.

[f] This CD8+ T cell epitope, with an amino acid substitution at position 5, has been identified in both SIVmac239- and SIVmac251-infected macaques.

[g] This CD8+ T cell epitope, with amino acid substitutions at position 7 and 8, has been identified in both SIVmac239- and SIVsmE660-infected macaques.

[h] This CD8+ T cell epitope, with an amino acid substitution at position 1, has been identified in both SIVmac239- and SIVmac251-infected macaques.

[i] The following GenBank Acc. No. is also listed for Mamu-A*02: AJ539308.
[j] Epitopes may also be restricted by Mamu-A*01 in addition to Mamu-A*02.
[k] SIVppm is a heterogenous virus stock that contained both sequences of this Nef epitope.
[l] This CD8+ T cell epitope, with an amino acid substitution at position 3, has been identified in both SIVmac239- and SIVppm-infected macaques.
[m] MHC class I restriction unknown but mapped to a single MHC class I haplotype, 90-120-Ia. This haplotype consists of three *Mamu-A* alleles, (*Mamu-A120-1*, *Mamu-A120-4*, and *Mamu-A120-5*) and four *Mamu-B* alleles (*Mamu-B120-1*, *Mamu-B120-6*, *Mamu-B120-8*, and *Mamu-B120-9*).
[n] The following GenBank Acc. No. is also listed for Mane-A*10: EF010518.

Table I-B-2: Known MHC class II epitopes and resticting molecules

Virus	Species[a]	Protein	Amino acid positions[b]	Short name	Sequence	Restricting molecule[c]	GenBank Acc. No.	Reference
SIVmac239	Rhesus	Gag	102-111 (103-112)	QE10 (IT10)	QIVQRHLVVE (IVQRHLVVET)	DRBw*606	AJ601370	Giraldo-Vela *et al.*, 2007
SIVmac239	Rhesus	Gag	184-193	YV10	YDINQMLNCV	DRBw*2104	AJ601362	Giraldo-Vela *et al.*, 2007
SIVmac239	Rhesus	Gag	197-211	GA15	QAAMQIIRDIINEEA	DRB1*0306	L27740	Giraldo-Vela *et al.*, 2007
SIVmac239	Rhesus	Gag	260-274	GC15	GNIYRRWIQLGLQKC	DRB*w201	L27742	Dzuris *et al.*, 2001
SHIV-89.6 SHIV-HXBc2	Rhesus	Env	172-191	EY20	EYAFFYKLDIIPIDNDTTSY	DRB*w201	L27742	Lekutis & Letvin, 1997; Lekutis *et al.*, 1997
SHIV-89.6 SHIV-HXBc2	Rhesus	Env	242-261	VL20	VSTVQCTHG**IRPVVSTQL**LL[d]	DRB1*0406	AJ601355	Dzuris *et al.*, 2001; Lekutis & Letvin, 1997
SHIV-89.6 SHIV-HXBc2	Rhesus	Env	486-494	YL9	**YKVVKIEPL**[d]	DRB*w201	L27742	Dzuris *et al.*, 2001; Lekutis & Letvin, 1997; Lekutis *et al.*, 1997
SIVmac239	Rhesus	Rev	11-23	RT13	RKRLRLIHLLHQT	DRB*w201	L27742	Dzuris *et al.*, 2001
SIVmac239	Rhesus	Rev	13-23	RT11	RLRLIHLLHQT	DPB1*06	EF490966	Giraldo-Vela *et al.*, 2007
SIVmac239	Rhesus	Nef	138-152	RI15	RHRILDIYLEKEEGI	DRBw*606	AJ601370	Giraldo-Vela *et al.*, 2007
SIVmac239	Rhesus	Vpx	31-40 (32-41)	EL10 (IP10)	EINREAVNHL (INREAVNHLP)	DRB1*1003	AJ601356	Giraldo-Vela *et al.*, 2007

Notes:

[a] Unless specified, rhesus designation implies rhesus macaques of Indian descent.

[b] Positions indicated for SIVmac239 or first virus listed for each epitope unless otherwise specified.

[c] MHC class I molecule designation: rhesus macaque (*Macaca mulatta*; Mamu).

[d] The core binding region is shown in bold [Dzuris *et al.*, 2001].

Table I-B-3: Peptide-binding motifs of macaque MHC molecules

MHC molecule	Primary anchor positions	Preferred amino acids	Tolerated amino acids	References
Mamu-A*01[a]	2[b] 3[b] C-terminus[b]	S T P F L I V M	F W Y N A G P L I V M T A C W Y T A	Allen *et al.*, 1998; Sidney *et al.*, 2000
Mamu-A*02[a]	2 C-terminus	T S V Y F M L W V I	L I V M A A	Loffredo *et al.*, 2004
Mamu-A*11[a]	2 C-terminus	E I	D M F W L M V	Sette *et al.*, 2005
Mamu-B*01[a]	2 C-terminus	D E I F L V W	A S N G I Q L T V M Y M	Loffredo *et al.*, 2005
Mamu-B*03 (preliminary motif)	2 C-terminus	R L		Dzuris *et al.*, 2000
Mamu-B*04 (preliminary motif)	2	G		Dzuris *et al.*, 2000
Mamu-B*08 (preliminary motif)	2 C-terminus	R L I V		Loffredo *et al.*, 2007c
Mamu-B*17[a]	2 C-terminus	H A M R F W	L P Q K S C W Y T G F Y	Mothé *et al.*, 2002b
Mamu class II DR supermotif[c]	1 6 9	L I V M A F Y L I V M F Y S T Q A L I V M F Q		Dzuris *et al.*, 2001

Notes:

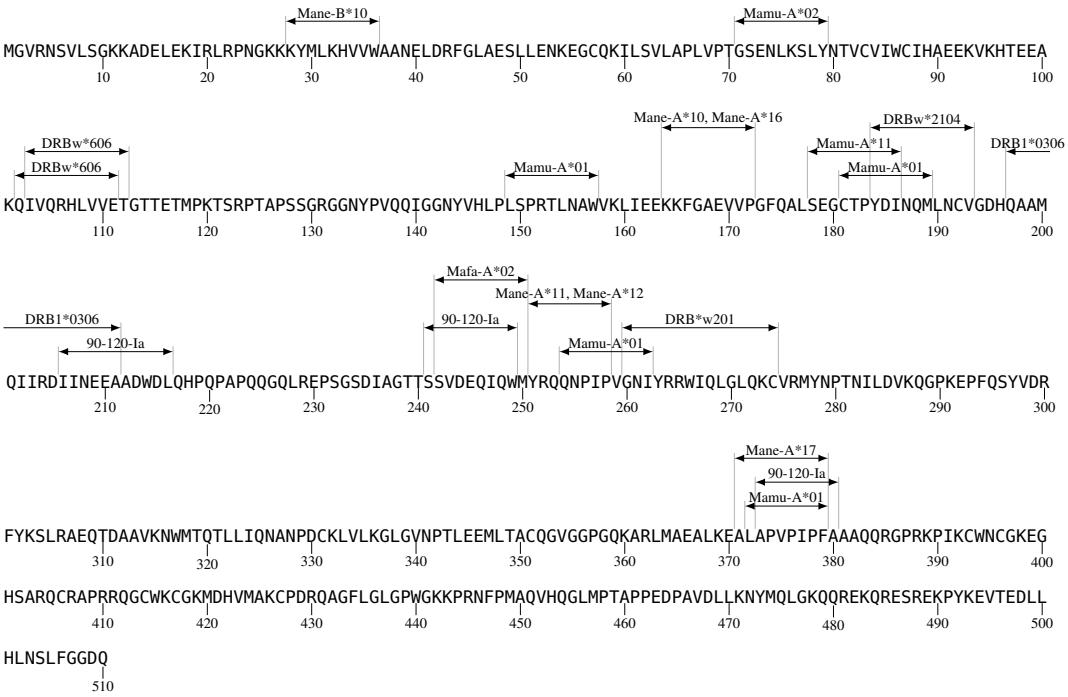
[a] A quantitative algorithm is also available for this allele at `http://www.mamu.liai.org/` [Peters *et al.*, 2005a].

[b] The Mamu-A*01 peptide-binding motif requires the presence of two of the three anchor positions for binding. Peptides can bind using P2/C-terminus or P3/C-terminus anchoring spacing.

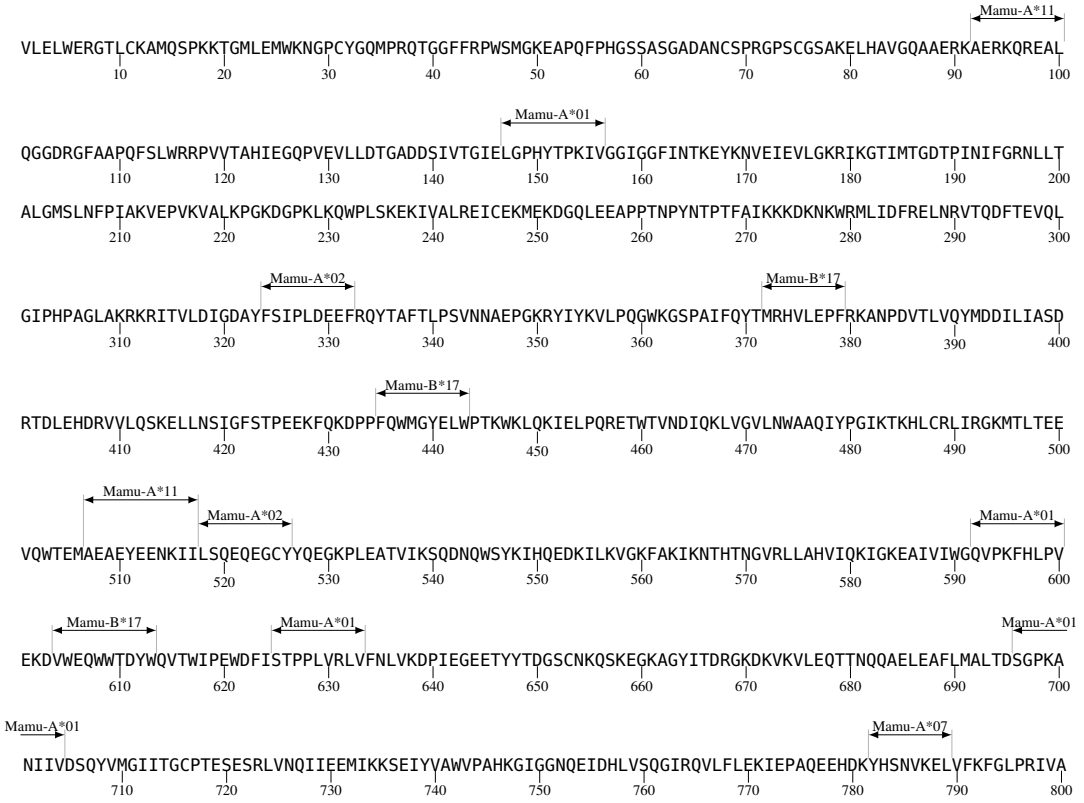
[c] Mamu class II DR supermotif is based on data from Mamu-DRB1*0406 and Mamu-DRB*w201 [Dzuris *et al.*, 2001].

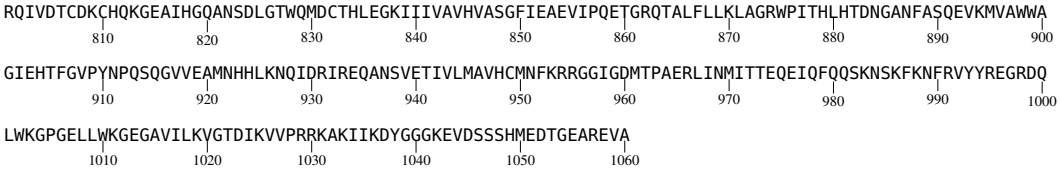
I-B-14 Map of SIV epitopes

Gag SIV Epitope Map

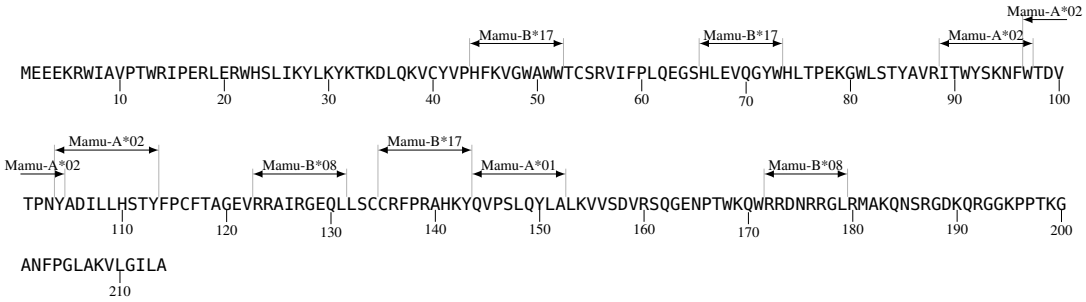


Pol SIV Epitope Map





Vif SIV Epitope Map



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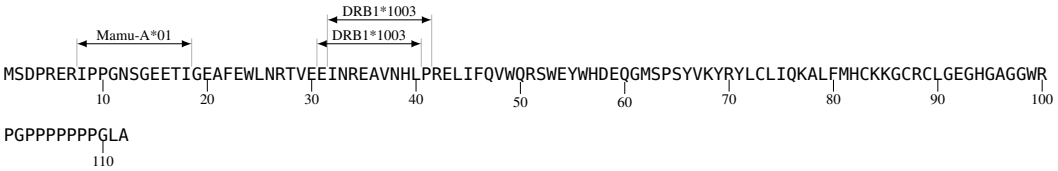

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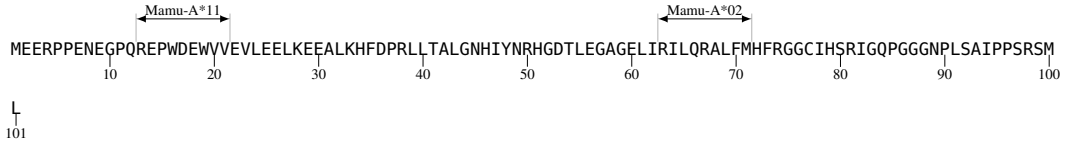

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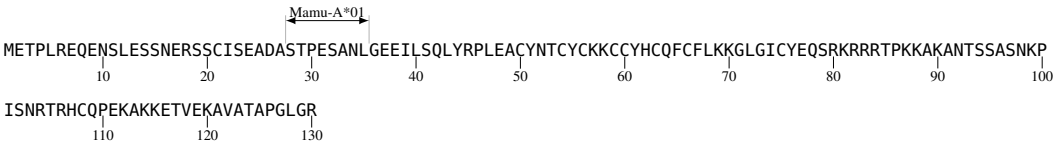
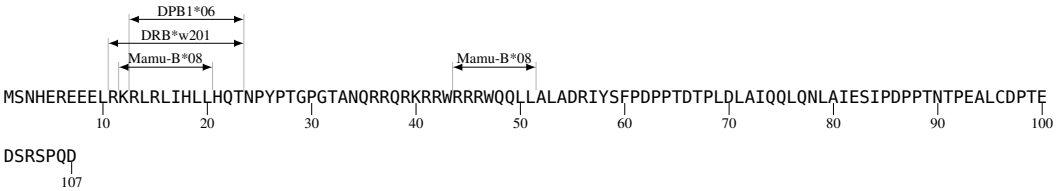
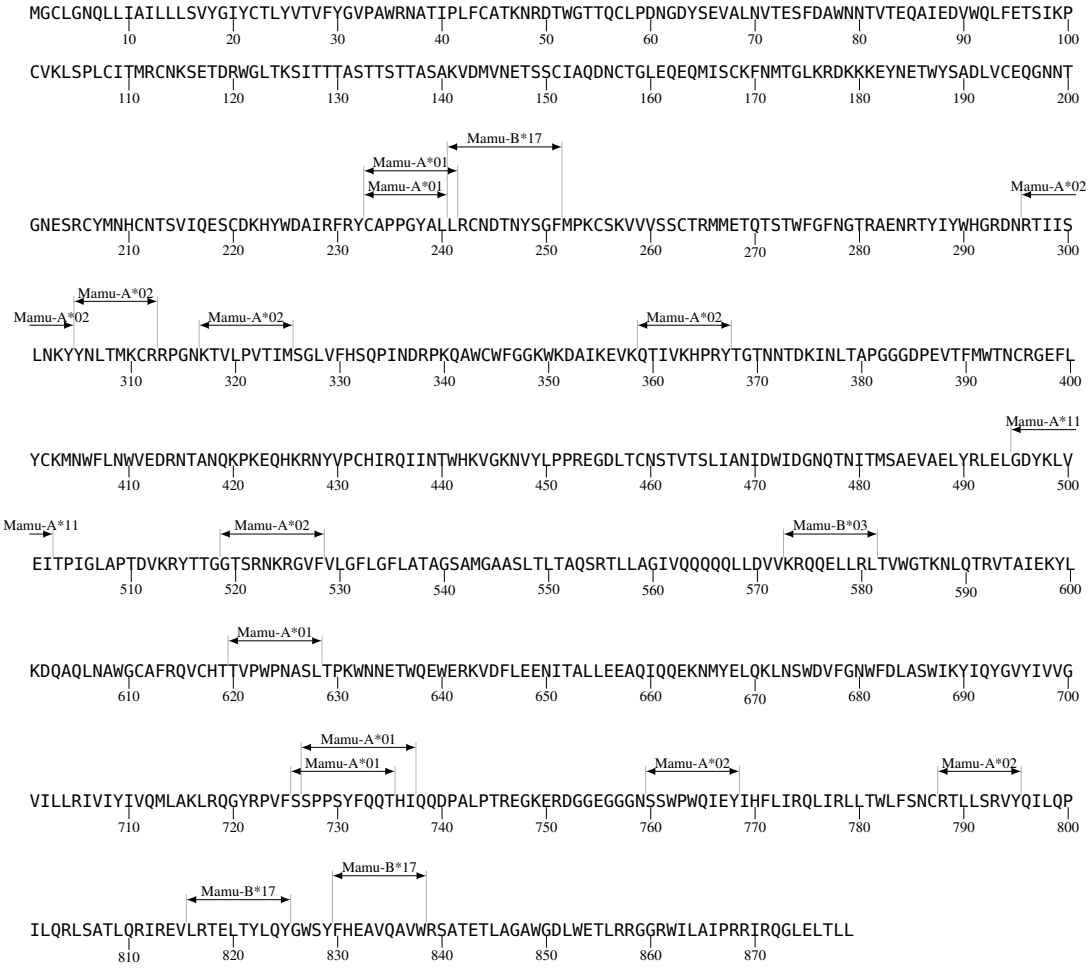


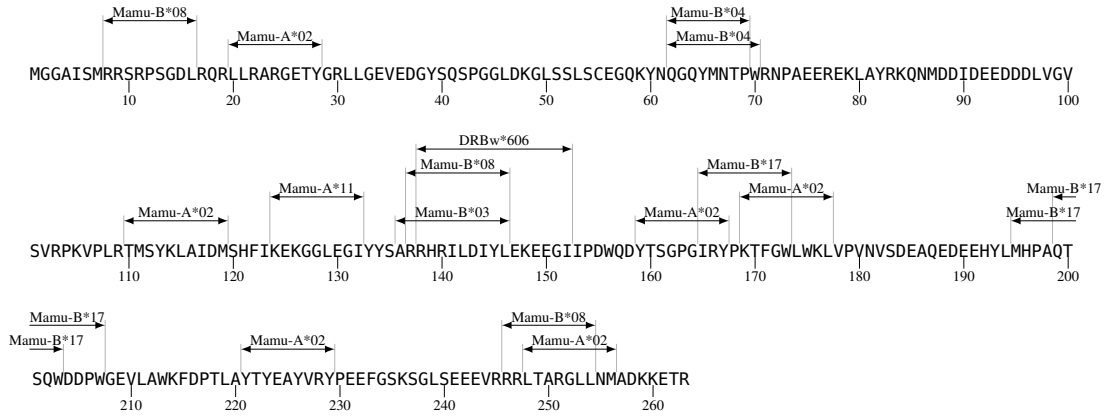
Rev SIV Epitope Map



Env SIV Epitope Map



Nef SIV Epitope Map



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