CTL Responses of Rhesus Monkeys to AIDS Viruses: Epitopes and Their Restricting MHC Class I Alleles

William A. Charini and Norman L. Letvin

Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02158, USA

Macaque species are proving to be crucially important animals for studying AIDS pathogenesis and exploring HIV vaccine strategies. In both of these experimental areas it is important to measure virus-specific CTL responses with precision. This can best be done with knowledge of epitopes and their restricting MHC class I alleles. We now begin categorizing these epitope-specific CTL responses. We only include those epitopes that have been published and those in which the MHC class I alleles that bind these peptides have been characterized. To date, this has only been done in *Macaca mulatta* (rhesus monkeys), although *M. nemestrina* (pig-tailed macaques) and *M. fascicularis* (crab-eating macaques) are frequently used in AIDS experimental work. Both the nucleotide and predicted amino acid sequences of the MHC class I alleles are shown. With the expanding use of SHIV constructs for these studies, we include CTL epitopes of both SIV and HIV-1 envelopes. We hope to maintain an up-to-date listing by adding newly defined epitopes as they become available. Please contact us with contributions at:

	Bette Korber	**William A. Charini**	**Norman L. Letvin**
phone:	505-665-4453	617-667-0250	617-667-2766
fax:	505-665-3493	617-667-8210	617-667-8210
email	btk@t10.lanl.gov	wcharini@bidmc.harvard.edu	nletvin@bidmc.harvard.edu

Table 1 CTL Epitopes

Viral protein	Epitope	Restricting MHC class I allele	GenBank Acc. No.	Reference
SIVmac	Gag CTPYDINQM	Mamu-A*01	U50836	Miller, et al. 1991 Allen et al., 1998 in press
SIVmac	Env YNLTMKCR	Mamu-A*02	U50837	Watanabe, et al. 1994
	EITPIGLAP	Mamu-B*01	U42837	Yasutomi, et al. 1995
HIV-1	Env KPCVKLTP	Mamu-B*12		Voss, et al. 1996
	NNLLRAIEA	Mamu-A*08		Voss, et al. 1996

Alignment of Sequences of Restricting Alleles

The nucleotide sequences of cDNA clones of the five MHC class I restricting alleles of rhesus monkey (*Macaca mulatta*) described in Table 1 are shown aligned below with their predicted amino acid sequences.

```
CONSENSUS CTCCTCCTGgTGCTCTC?GGGgCcCTGgcCCTGACccAGACCtGGGCcGGCTCgCACTCCaTGAgGTATTTCtaC     74
Mamu-A*01 -----------------A----------T-------------C----G-----T----------A----------     75
Mamu-A*02 -----------------A-----------------T------C----A-----T--------------------     75
Mamu-A*08 -----------------C-----G-----------------------------------T--------------     75
Mamu-B*01 ---------C-------G-------------------------------------------------------C--     75
Mamu-B*12 ---------C-------G---A-----T--------G-----------------------------------AG-     75
          -> leader peptide                                -> alpha 1 domain
CONSENSUS _L__L__L__v__L__S__G__a__L__a__L__T__q__T__w__A__G__S__H__S__m__r__Y__F__y_     25
Mamu-A*01 ----------------------------V--------------R--------------------K----------     25
Mamu-A*02 -------------------------------------------R------------------------------     25
Mamu-A*08 -------------------------------------------------------------L-------------     25
Mamu-B*01 ----------L-----------------------------------------------------------------H-     25
Mamu-B*12 ----------L-----------T-----S--------E-----------------------------------S-     25

CONSENSUS ACc?CcgTGTCCCGGCCCGGCCGCgGGgAgCCCcGcTtcaTCgccGTgGGCTACGTGGACGACACGCAGTTCGTG    148
Mamu-A*01 ---T--A--------------------C-----------------------------------------------    150
Mamu-A*02 ---T--A-----------------T-----------------------------------------------------    150
Mamu-A*08 ---G-----------------------C--------------T------------------------------    150
Mamu-B*01 --GC--------------------------------------T------------------------------    150
Mamu-B*12 ---G-A------------------C----A---T-G-ATC---AA--C---------------------------    150

CONSENSUS _T__?__v__S__R__P__G__R__g__e__P__r__f__i__?__V__G__Y__V__D__D__T__Q__F__V_     48
Mamu-A*01 ----S--M--------------------Q--------------A------------------------------     50
Mamu-A*02 ----S--M-----------------W-----------------A------------------------------     50
Mamu-A*08 ----A-----------------------Q--------------S------------------------------     50
Mamu-B*01 ----P--------------------------------------S------------------------------     50
Mamu-B*12 ----A--------------------R--------W--Y--L--E------------------------------     50

CONSENSUS CGgTTCGACAGCGACGCCGaGAGtC?gAGgatGGAGCCGCGGGCGCCgTGGgTgGAGCAGGAGGGgCCgGAGTAT    222
Mamu-A*01 -------------------C---C-AA-------------------------------------T---------    225
Mamu-A*02 -------------------C---C-A--------------------------------------T--A------    225
Mamu-A*08 -------------------------C---AGA-----------------------------------------    225
Mamu-B*01 --A----------------------G---------------------C---A-A---------------------    225
Mamu-B*12 -------------------------C-----------------------------------------------    225

CONSENSUS _R__F__D__S__D__A__e__S__?__R__m__E__P__R__A__P__W__v__E__Q__E__G__P__E__Y_     72
Mamu-A*01 -------------------A-----Q-----------------------------------------------     75
Mamu-A*02 -------------------A-----Q-----------------------------------------------     75
Mamu-A*08 -------------------------P-----E-------------------------------------------     75
Mamu-B*01 -------------------------R-------------------------I----------------------     75
Mamu-B*12 -------------------------P-----------------------------------------------     75
```

```
CONSENSUS TGGGAccgGgAgACACGGAac??cAAGgcCgagaCACAGAatgaCCgAGtGaaCCTGcgGAaCctGCgC?GCTAC    294
Mamu-A*01 ---------------------ATG---A---------------C--C--------------C-----T-C-----    300
Mamu-A*02 ---------------------ATG-------------------C--C----------------------G-----    300
Mamu-A*08 ---------A-C-------T-TA--------C---------CT------A-GG-----A----------G-----    300
Mamu-B*01 --------------------GGC-----G-A-CG------C--------A-----------T-GC--T-A-----    300
Mamu-B*12 -----AGA-C-----------GC-------A-CG------C-----------G----G-----------C-----    300

CONSENSUS _W__d__r__e__T__R__n__?__K__a__?__t__Q__n__?__r__v__n__L__r__n__l__r__?__Y_     93
Mamu-A*01 ----------------------M-----T--E-----------A--P--------------T-----L--R----    100
Mamu-A*02 ----------------------M--------E-----------A--P-----------------------G----    100
Mamu-A*08 ----------N--------I--Y--------A-----------Y-----E--G-----Q-----------G----    100
Mamu-B*01 -------------------K--A-----G--N--A-----T--D-----E-----------I--A--L--S----    100
Mamu-B*12 ----E--E--Q-----------A--------N--A-----T--D--------S-----G-----------R----    100

CONSENSUS TACAACCAGAGCGAGgccGGGTCtCACACc?tCCAGA?gATGtacGGCTGCGACCTGGGgCCcGACGGGCGCCTC    367
Mamu-A*01 ------------------------------C------G----GTT-------------------------------    375
Mamu-A*02 ------------------------------A------G-----------------------G------------    375
Mamu-A*08 -----------------------C------TA-----C-----------------------A------------    375
Mamu-B*01 ---------------A-G------------C------T----C----------------A---------------    375
Mamu-B*12 ----------------GG-----------TG------TA--------------------A---------------    375
                              -> alpha 2 domain
CONSENSUS _Y__N__Q__S__E__a__G__S__H__T__?__Q__?__M__y__G__C__D__L__G__P__D__G__R__L_    116
Mamu-A*01 ------------------------------L-----R-----V-------------------------------    125
Mamu-A*02 ------------------------------I-----R-----------------------------------    125
Mamu-A*08 ------------------------------Y-----T-----------------------------------    125
Mamu-B*01 ----------------T--------------L-----M-----H-------------------------------    125
Mamu-B*12 ----------------G--------------V-----I-----------------------------------    125

CONSENSUS CTCCGCGGGTAT?AcCAGt?CGCCTACGACGGCAaGGATTACATCGCCCTGAACGAGGACCTGCgCTCCTGGACc    440
Mamu-A*01 ------------G-A----A-------------------------------------------------------    450
Mamu-A*02 ------------C------C-------------------------------------------------------    450
Mamu-A*08 ------------G------C--------------G--------------------------------------G    450
Mamu-B*01 ------------T-----CG-----------------------------------------A----------    450
Mamu-B*12 ------------C------T-------------------------------------------------------    450

CONSENSUS _L__R__G__Y__?__Q__?__A__Y__D__G__k__D__Y__I__A__L__N__E__D__L__r__S__W__T_    139
Mamu-A*01 -------------E-----Y-------------------------------------------------------    150
Mamu-A*02 -------------H-----S-------------------------------------------------------    150
Mamu-A*08 -------------D-----S--------------R--------------------------------------    150
Mamu-B*01 -------------Y-----R-----------------------------------------H----------    150
Mamu-B*12 -------------H-----F-------------------------------------------------------    150

CONSENSUS GCcGCGGACaTGGCgGCTCAGAACACCCAGCGcAAGTGGGAGGcGGcgggTgagGCgGAGcgg?tcAGAgCCTAc    514
Mamu-A*01 --G------G-------------------------------------A--T-------A-CA-G---------    525
Mamu-A*02 ------------------------------------------------------------A-CA----A-----    525
Mamu-A*08 --A-----------T-----------------------------------------------T-----A-----    525
Mamu-B*01 ---------T----------------------G--------------C----T---A----A-CGG---------    525
Mamu-B*12 -------------------------------------------G--ACC--T-T---------T----------T    525

CONSENSUS _A__A__D__m__A__A__Q__N__T__Q__R__K__W__E__a__a__g__?__A__E__?__?__R__a__Y_    161
Mamu-A*01 ----------V-------------------------------------D--V--------S--M----------    175
Mamu-A*02 -----------------------------------------------E--------Q--H-----T----    175
Mamu-A*08 -----------------------------------------------E--------R--F-----T----    175
Mamu-B*01 ----------L-----------------------------------V--------Q--R----------    175
Mamu-B*12 -------------------------------------------G--D--R--Y--------R--F----------    175
```

```
CONSENSUS CTGGAGGGCcaGTGCgTGGAGTGGCTCCgCAGATAcCTGGAGAAcGGGAAGGAGACgCTGCAGCGCgCGGAcCCC    589
Mamu-A*01 ----------------------------C---------------G---------------------A--------    600
Mamu-A*02 ---------G-----C-------------------------------------------------------------    600
Mamu-A*08 ---------G-------------------------T-------------------------------------------    600
Mamu-B*01 ----------G--------------------------------G-----------A------------------    600
Mamu-B*12 ----------G-------------------------------------------------------------T---    600
                                                                alpha 3 domain ->
CONSENSUS _L__E__G__?__C__v__E__W__L__r__R__Y__L__E__n__G__K__E__T__L__Q__R__a__D__P_    185
Mamu-A*01 ----------Q-----------------P--------------K-----------------------T-------    200
Mamu-A*02 ----------E-----L-------------------------------------------------------------    200
Mamu-A*08 ----------E-------------------------------------------------------------------    200
Mamu-B*01 ----------R-------------------------------K-------------------------------    200
Mamu-B*12 ----------R-------------------------------------------------------------------    200

CONSENSUS CCcAAGACACAcGTGACCCACCACCCcGTCTCTgACCAtGAGgCCAcCCTGAGGTGCTGGGCCCTGGGCTTCTAC    664
Mamu-A*01 -----------T-------------------------------------------------------------------    675
Mamu-A*02 -----------T--------------------------A----------------------------------------    675
Mamu-A*08 -------------------------------------------------------------------------------    675
Mamu-B*01 --A-----------------------T---------------A---T----------------------------    675
Mamu-B*12 --A------------------------------A-------------------------------------------    675

CONSENSUS _P__K__T__H__V__T__H__H__P__V__S__d__h__E__a__t__L__R__C__W__A__L__G__F__Y_    210
Mamu-A*01 -------------------------------------------------------------------------------    225
Mamu-A*02 -------------------------------------Q-----------------------------------------    225
Mamu-A*08 -------------------------------------------------------------------------------    225
Mamu-B*01 ---------------------------------------------T--I----------------------------    225
Mamu-B*12 ----------------------------------N-------------------------------------------    225

CONSENSUS CCTGcGGAGATCACACTGACCTGGCAGCGGGATGGgGAGGACCAAACTCAGGACACgGAGCTcGTGGAGACCAGG    739
Mamu-A*01 -------------------------------------------------------------------------------    750
Mamu-A*02 -----------------------------------A-------------------------------------------    750
Mamu-A*08 -------------------------------------------------------------------------------    750
Mamu-B*01 -------------------------------------------------------------T-----T------------    750
Mamu-B*12 ----T-------------------------------------------------------C------------------    750

CONSENSUS _P__a__E__I__T__L__T__W__Q__R__D__G__E__D__Q__T__Q__D__T__E__L__V__E__T__R_    235
Mamu-A*01 -------------------------------------------------------------------------------    250
Mamu-A*02 -------------------------------------------------------------------------------    250
Mamu-A*08 -------------------------------------------------------------------------------    250
Mamu-B*01 -------------------------------------------------------------------------------    250
Mamu-B*12 ----V-------------------------------------------------------------------------    250

CONSENSUS CCtGcAGGaGAtGGAACCTTCCAGAAgTGGGcgGCTGTGGTGGTGCCTTCTGGAgAgGAGCAGAGATACACcTGt    814
Mamu-A*01 -------------------------------------------------------------------------------    825
Mamu-A*02 --------G--C-------------------------------------------A--------------------    825
Mamu-A*08 -------------------------------------------------------A--------------------    825
Mamu-B*01 --A-G---------------------A----GA-----------------------A--------------G--C    825
Mamu-B*12 --A-G--------------------------GA-----------------------A--------------G--C    825

CONSENSUS _P__a__G__D__G__T__F__Q__K__W__a__A__V__V__V__P__S__G__e__E__Q__R__Y__T__C_    260
Mamu-A*01 -------------------------------------------------------------------------------    275
Mamu-A*02 -------------------------------------------------------------K------------------    275
Mamu-A*08 -------------------------------------------------------------K------------------    275
Mamu-B*01 ----G--------------------------G-------------------------------------------    275
Mamu-B*12 ----G--------------------------G-------------------------------------------    275
```

```
CONSENSUS CATGTGCAGCATGAGGGtCTGCc?gAGCCCCtCACCCTGAgATGGGAGCCgTcTTCCCAGTCCACCATCCcCATc    888
Mamu-A*01 -----------------------CA------A--------A-----------T--------------------G    900
Mamu-A*02 ----------------------GT-----------------------------------------------T----    900
Mamu-A*08 -----------------------C-----------------------------------------------------G    900
Mamu-B*01 -----------------G-----G--------------------------A------------------------    900
Mamu-B*12 -----------------G-----A--------------------------A------------------------    900
                                                   -> transmembrane domain
CONSENSUS _H__V__Q__H__E__G__L__p__e__P__l__T__L__r__W__E__P__s__S__Q__S__T__I__p__i_    285
Mamu-A*01 -------------------------K-----H--------K-----------F--------------------M-    300
Mamu-A*02 ----------------------R-----------------------------------------------L----    300
Mamu-A*08 ---------------------------------------------------------------------------M-    300
Mamu-B*01 ---------------------------------------------------------------------------    300
Mamu-B*12 ---------------------------------------------------------------------------    300

CONSENSUS GTGGGCATCaTTGCTGGCCTGGtTctCCTtGgAgtTGTGGTCActGGAGCTGTGgTcGCTGCTGTGATgTGGAGG    963
Mamu-A*01 ----------------------------------C---------------------T------------------    975
Mamu-A*02 ----------------------------------A---------T----------A-T-----------A------    975
Mamu-A*08 ----------------------------------C----------------------------------------    975
Mamu-B*01 ---------G------------C-G----A-C------------C------------------------------    975
Mamu-B*12 ---------G------------C-GG---A-C------------C------------------------------    975

CONSENSUS _V__G__I__i__A__G__L__v__l__L__g__?__V__V__t__G__A__V__v__A__A__V__m__W__R_    309
Mamu-A*01 ----------------------------------A----------------------------------------    325
Mamu-A*02 ----------------------------------I--------I-----------I-----------I-------    325
Mamu-A*08 ----------------------------------A----------------------------------------    325
Mamu-B*01 ----------V-----------A--V-----A--V----------------------------------------    325
Mamu-B*12 ----------V-----------A--G-----A--V----------------------------------------    325

CONSENSUS AGGAAGAGCTCAGaTaGAAAAGGAGGGAGCTACTCTCAGGCTGCaagCAgtGACAGTGCCCAGGGCTCTGATGTG   1038
Mamu-A*01 ---------------------------------------------------------------------------   1050
Mamu-A*02 ---------------------------------------------------------------------------   1050
Mamu-A*08 ---------------------------------------------------------------------------   1050
Mamu-B*01 -------------G-G----------------------------GTC---C------------------------   1050
Mamu-B*12 -------------G-G----------------------------GTC--AC------------------------   1050
                     -> cytoplasmic domain
CONSENSUS _R__K__S__S__d__r__K__G__G__S__Y__S__Q__A__A__S__s__D__S__A__Q__G__S__D__V_    334
Mamu-A*01 ---------------------------------------------------------------------------    350
Mamu-A*02 ---------------------------------------------------------------------------    350
Mamu-A*08 ---------------------------------------------------------------------------    350
Mamu-B*01 -------------G--G-----------------------------------------------------------    350
Mamu-B*12 -------------G--G--------------------------------N------------------------    350

CONSENSUS TCTCTCACGGCTTgtAAAGTGTGA                                                      1062
Mamu-A*01 ------------------------                                                      1074
Mamu-A*02 ------------------------                                                      1074
Mamu-A*08 ------------------------                                                      1074
Mamu-B*01 -------------AA                                                               1065
Mamu-B*12 --------------A                                                               1065

CONSENSUS _S__L__T__A__c__K__V__$_                                                       341
Mamu-A*01 ------------------------                                                       357
Mamu-A*02 ------------------------                                                       357
Mamu-A*08 ------------------------                                                       357
Mamu-B*01 -------------$-                                                                354
Mamu-B*12 -------------$-                                                                354
```

References

[1] Allen, T. M., J. Sidney, M-F del Guercio, 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 SIV. *J. Immunol.* (in press).

[2] 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 T lymphocytes in SIVmac-infected rhesus monkeys. *J. Immonol.* **147**:320–329.

[3] 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. *J. Virol.* **70**:7335–7340.

[4] 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. *J. Virol.* **68**:6690–6696.

[5] 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. *J. Immunol.* **154**:2516–2522.