PART III: HELPER T-CELL EPITOPES

SUMMARY

Part III includes tables and maps of HIV-specific helper T-cell (Th) epitopes arranged sequentially according to the location of the proteins in the HIV-1 genome. We attempted to make this section as comprehensive as possible, requiring that the epitope be contained within a region of 30 amino acids maximum, but not that the precise boundaries be defined. The HLA specificity is usually not determined for Th epitopes. For more recent updates, epitope sequence alignments, and useful searching capabilities, please see our web site: http://hiv-web.lanl.gov/immunology. The same epitope can have multiple entries, as each entry represents a single publication. Helper T-cell responses to proteins with no defined epitope are described at the end of each protein section.

A. TABLES:

Each Th epitope has a six-part basic entry:

- **HXB2 Location:** The viral strain HXB2 is used as a reference strain throughout this publication. The position of the defined epitope location on the sequence of the HXB2 protein is indicated. Obviously HXB2 may not be identical to a given defined reactive sequence, so we simply indicate the location of the aligned positions. The HXB2 numbering is used in to the protein maps of this database.
- **Author Location:** The amino acid positions of the epitope boundaries and the reference sequence are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases the reference sequence identification was not provided, and in such cases it is not possible to use these numbers to specify precise locations. If you are interested in finding the precise positions of epitopes you are studying, please try using the interactive position locator at our web site: http://hiv-web.lanl.gov/NUM-HXB2/HXB2.MAIN.html.
- **Epitope Sequence:** The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On rare occasions, when only the epitope location and not the actual epitope was specified in the original publication, if the sequences were numbered inaccurately by the primary authors, we may have misrepresented the epitope's amino acid sequence. Therefore, epitopes that were not explicitly written out in the text in the primary publication, those that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.
- **Immunogen:** The antigenic stimulus of the Th response to the defined epitope.
- **Species(HLA):** The species responding and HLA specificity of the epitope, when known.
- **Reference:** The primary reference.

Following each entry for a given Th epitope is a brief comment explaining the context of the study that defined or studied the epitope. If the same response to an epitope was studied in several labs, each study is cited in its own entry.

B. HIV PROTEIN EPITOPE MAPS:

All human and primate Th epitopes defined to within 21 amino acids or less are indicated on the HIV protein epitope maps. HLA restriction information is included when known.

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

ALIGNMENTS:

Alignments that correspond to the epitopes are only available from the Web site, not in the hard copy of the compendium, due to space limitations. All epitopes are aligned to the HXB2 sequence, with the sequence used to define the epitope indicated directly above it. In consensus sequences an upper case letter indicates the amino acid was present in all sequences, a lower case letter indicates the amino acid was present in most sequences in a given position, and a question mark indicates two or more amino acids were represented with equal frequency. The master alignment files from which the epitope alignments were created are available from our Web site at (http://hiv-web.lanl.gov/ALIGN_CURRENT/ALIGN-INDEX.html), and we restricted our-

selves to full gene region sequences for these alignments, excluding short fragments of sequences. The subtype designation and the country of isolation are indicated along with the common name of the sequence. The alignments were modified in some cases to optimize the alignment relative to the defined epitope and minimize insertions and deletions. A dash indicates the same amino acid is found in the HXB2 sequence, and a period indicates an insertion made to maintain the alignment. Stop codons are indicated with a $, and frameshifts by a #; they are inserted to maintain the alignments.

C. REFERENCES AND NOTES

Part III-A: Table of Helper T-cell Epitopes

All Helper T-cell epitopes 30 amino acids or less in length arranged by protein position

Table 1: **p17**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p17(21–35)	p17(21–35 SF2)	LRPGGKKKYKLKHIV	HIV-1 infection	human(DR13.02)	[Harcourt1998]
	• 43 asymptomatic HIV+ individuals were screened for proliferative responses to HIV – 12 showed a response, and dominant epitopes were mapped for two individuals, one in p24 and one in p17 • Patient 024's naturally occurring variant LRPGGKKKYQLKHIV also elicited a strong proliferative response. • Other variants of this epitope were found within the individual who made this response – several did not stimulate the CD4+ T-cell line that recognized the index peptide, suggestive of immune escape				
p17(22–29)	p17(22–29 LAI)	RPGGKKKY?	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors • Schrier lists this peptide as p24(22-29), but we placed it in p17				
p17(33–47)	p17(33–47 IIIB B10)	HIVWASRELERFAVN?	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• Peptides were identified that commonly evoke Th cell responses – 57% of 90 HIV+ people had a T-cell response to this peptide				
p17(93–107)	p17(93–107 IIIB B10)	EIKDTKEALDKIEEE	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses				
p17(118–132)	p17(118–132 IIIB B10)	AAADTGHSSQVSQNY	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• 12 gag and 18 env Th cell sites were identified that could commonly evoke T-cell responses				

Table 2: **p24**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p24(1–11)	p24(1–11 SF2)	PIVQNLQGQMV	HIV-1 infection	human(DR1)	[Harcourt1998]
	• 43 asymptomatic HIV+ individuals were screened for proliferative responses to HIV – 12 showed a response, and dominant epitopes were mapped for two individuals, one in p24 and one in p17 • Out of five truncated versions of peptide PIVQNLQGQMVHQAISPRTL, only p24-1/11 elicited a proliferative response • Nine naturally occurring variants of this epitope were found within the individual who made this response – all bound to HLA-DR1, but three did not stimulate the CD4+ T-cell line that recognized the index peptide, suggestive of immune escape				
p24(1–15)	p24(133–147 IIIB B10)	PIVQNIQGQMVHQAI	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• Peptides were identified that commonly evoke T-cell responses – 62% of 90 HIV+ people had a T-cell response to this peptide				
p24(1–22)	p24(133–154 SF2)	PIVQNIQGQMVHQAIS-PRTLNA	HIV-1 infection	human( )	[Rosenberg1997]
	• While anti-HIV CD4 Th responses are characteristically undetectable in chronic infections, strong p24-specific proliferative responses were inversely correlated with low viral load in 10 chronically infected people • The dominant proliferative response in one of two long term survivors was to this peptide				
p24(7–21)	Gag(171–185)	QGQMVHQAISPRTLN	HIV-1 infection	human(DR supermotif)	[Wilson2001]
	• Epitope name: Gag 171. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors • This epitope binds to nine HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRBI*0405, DRB1*1302, DRB1*0701, DRB1*0901, DRB5*0101 and DRB4*0101 with an IC50 threshold below 1,000 nM • This epitope sequence is conserved in 52% of clade B isolates • 7/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)				
p24(11–26)	p24(143–157)	VHQAISPRTLNAWVKC	*in vitro* stimulation	human( )	[Bedford1997a]
	• Epitope elicits a primary proliferative response in PBMC from uninfected donors • Matches 3/3 anchor residues for HLA DR: **V**HQAI**S**PR**T**				
p24(11–30)	p24(143–162 HXB2)	VHQAISPRTLNAWVK-VVEEK	Vaccine	murine(H-2^d, H-2^b)	[Mata1999]
	Vaccine: *Vector/type: Listeria monocytogenes* *Strain:* HXB2 *HIV component:* Gag • BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag • *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways				

- The class II T-helper response was probed using 20 mer peptides that overlapped by 10, and the peptides VHQAISPRTLNAWVKVVEEK and FRDYVDRFYKTLRAEQASQD were recognized in H-2^b and H-2^d mice

p24(11–30)	Gag(143–152 SF2)	VHQAISPRTLNAWVKVVEEK	Vaccine	murine(H-2d and H-2b)	[Mata1999]

Vaccine: *Vector/type:* Listeria moncytogenes *Strain:* SF2 *HIV component:* p24

- Listeria moncytogenes is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response
- Listeria moncytogenes vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T-cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice
- Two of three reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains – this epitope is immunodominant in C57BL/6 mice and also can stimulate a BALB/c response
- The proliferative response is due to CD4+, IFN-γ producing cells, a Th1 response

p24(21–36)	p24(153–167)	NAWVKVVEEKAFSPEC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

p24(31–46)	p24(163–177)	AFSPEVIPMFSALSEC	*in vitro* stimulation	human(A*0201)	[Bedford1997a]

- Elicits a primary proliferative response in PBMC from uninfected donors
- Peptide contains a CTL epitope identified in HIV-positive patients
- Peptide binds to HLA A*0201 and causes regulation of class I expression on T2 cells
- Matches 3/3 anchor residues for HLA DR: **V**IPMF**S**AL**S**

p24(31–52)	p24(163–184 SF2)	AFSPEVIPMFSALSEGATPQDL	HIV-1 infection	human( )	[Rosenberg1997]

- Low viral load correlated with strong HIV-1-specific proliferative response
- A proliferative response to this epitope was detected in two long term survivors

p24(41–56)	p24(173–187)	SALSEGATPQDLNTMC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

p24(48–62)	p24(180–194)	TPQDLNTMLNTVGGH	HIV-1 infection	human( )	[Adams1997]

- One of four immunogenic Gag peptides used in study of proliferative response to p24
- Homology to an SIV epitope recognized by macaque T-cells
- T-cells from 8/19 HIV+ individuals responded to this epitope
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) increased detection of proliferative response

p24(51–66)	p24(183–197)	DLNTMLNTYGGHQAAC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

p24(51–82)	Gag(183–214 LAI)	DLNTMLNTVGGHQAA-MQMLKETINEEAAEWD-R	Vaccine	human( )	[Gahery-Segard2000a]

Vaccine: *Vector/type:* lipopeptide

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 2/10 reacted to this peptide
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual
- None of the 12 tested had an IgG response to this peptide

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p24(71–86)	p24(203–217)	ETINEEAAEWDRVHPC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

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p24(76–85)	p24(208–217)	EAAEWDRVHP	HIV-1 infection	human( )	[Adams1997]

- One of four immunogenic Gag peptides used in study of the proliferative response to p24
- T-cells from 11 of 24 HIV+ individuals responded to this epitope
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) increased detection of proliferative response

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p24(76–90)	p24(208–222 IIIB B10)	EAAEWDRVHPVHAGP	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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p24(81–95)	p24(215–229 SF2)	DRVHPVHAGPIAPGQ	Vaccine	macaque( )	[Mills1990]

Vaccine: *Vector/type:* virus-like particle *Strain:* SF2 *HIV component:* p24

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques

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p24(81–102)	p24(213–234 SF2)	DRVHPVHAGPIAPGQ-MREPRGS	HIV-1 infection	human( )	[Rosenberg1997]

- While anti-HIV CD4 Th responses are characteristically undetectable in chronic infections, strong p24-specific proliferative responses were inversely correlated with low viral load in 10 chronically infected people
- The dominant proliferative response in one of two long term survivors was to this peptide

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p24(87–101)	p24(219–233 BRU)	HAGPIAPGQMREPRG	*in vitro* stimulation	murine(H-2^b)	[Vaslin1994]

- Epitope name: Peptide G2. could prime for *in vitro* immunoproliferative responses and for subsequent IgG responses

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p24(96–103)	p24(228–235 LAI)	MREPRGSD	HIV-1 infection	human( )	[Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

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p24(96–110)	p24(228–242 IIIB B10)	MREPRGSKIAGTTST	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

p24(101–115)	p24(235–249 SF2)	GSDIAGTTSTLQEQI	Vaccine	macaque( )	[Mills1990]

Vaccine: *Vector/type:* virus-like particle *Strain:* SF2 *HIV component:* p24

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques – epitope response defined by T-cell clone

p24(101–116)	p24( )	GSDIAGTTSTLQEQIC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

p24(111–132)	p24(243–264 SF2)	LQEQIGWMTNNPPIPV-GEIYKR	HIV-1 infection	human( )	[Rosenberg1997]

- Low viral load correlated with strong HIV-1-specific proliferative response
- A proliferative response to this epitope was detected in two long term survivors

p24(119–133)	p24(251–265)	TNNPPIPBGEIYKRW	HIV-1 infection	human(DRB1*1301)	[Blankson2001, Malhotra2001]

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFNγ secretion and stronger proliferative responses against p24 80 weeks post-treatment
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (LTNPs) (it was in 9/18 50%, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay
- Two distinct DRB1*13 epitopes were defined in the peptide region spanning 251 to 270, and this 20-mer bound with very high affinity to DRB1*1302 – DRB1*1301 and DRB1*1302 would be expected to have very similar binding properties

p24(121–136)	p24(253–267)	NPPIPVGEIYKRWIIC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

p24(121–140)	p24(253–272 HXB2)	NPPIPVGEIYKRWIILG-LNK	Vaccine	murine(H-2^d)	[Mata1999]

Vaccine: *Vector/type: Listeria monocytogenes* *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways
- The class II T-helper response was probed using 20 mer peptides that overlapped by 10, and the peptide MPPIPVGEIYKRWIILGLNK gave the immunodominant response for the H-2^d haplotype, but was not recognized in H-2^b mice

p24(121–140)	Gag(253–272 SF2)	NPPIPVGEIYKRWILGL-NK	Vaccine	murine(H-2d)	[Mata1999]

Vaccine: *Vector/type:* Listeria moncytogenes *Strain:* SF2 *HIV component:* p24

- Listeria moncytogenes is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response
- Listeria moncytogenes vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T-cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice
- Two of three reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains – this epitope is immunodominant in BALB/c mice and did not stimulate a C57BL/6 response
- The proliferative response is due to CD4+, IFN-γ producing cells, a Th1 response

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p24(121–152)	Gag(183–214 LAI)	NPPIPVGEIYKRWIILG-LNKIVRMYSPTSILD	Vaccine	human( )	[Gahery-Segard2000a]

Vaccine: *Vector/type:* lipopeptide

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 9/10 reacted to this peptide
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in four vaccinees
- All of the 12 tested had an IgG response to this peptide

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p24(127–140)	Gag(294–308)	GEIYKRWIILGLNKI	HIV-1 infection	human(DR supermotif)	[Wilson2001]

- Epitope name: Gag 294. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicted proliferative responses from multiple HIV-infected donors
- This epitope binds ten HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101 with an IC50 threshold below 1,000 nM
- This epitope sequence is conserved in 95% of clade B isolates
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

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p24(128–137)	p24(260–269)	EIYKRWIILG	HIV-1 infection	human(DRB1*1301, DRB1*1302)	[Blankson2001, Malhotra2001]

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFNγ secretion and stronger proliferative responses against p24 80 weeks post-treatment
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)

- The truncated peptide that gave the optimal proliferative response for a Th1 phenotype clone was this nine-mer
- This region, shared by 2 overlapping peptides, was the reactive region for clones from two DRB1*13 patients, one carried DRB1*1301 and one DRB1*1302
- Two distinct epitopes were defined in the peptide region spanning 251 to 270, and this 20-mer bound with very high affinity to DRB1*1302 – DRB1*1301 and DRB1*1302 would be expected to have very similar binding properties

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p24(131–145)	p24(265–279 SF2)	KRWIILGLNKIVRMY	Vaccine	macaque( )	[Mills1990]

Vaccine: *Vector/type:* virus-like particle *Strain:* SF2 *HIV component:* p24

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques – epitope response defined by T-cell clone

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p24(131–145)	Gag(298–312)	KRWIILGLNKIVRMY	HIV-1 infection	human(DR supermotif)	[Wilson2001]

- Epitope name: Gag 298. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors
- This epitope binds thirteen HLA-DR alleles: DRB4*0101, DRB5*0101, DRB1*0901, DRB1*0802, DRB1*0701, DRB1*1302, DRB1*1201, DRB1*1101, DRB1*0405, DRB1*0401, DRB*0301, DRB1*1501 and DRB1*0101, with an IC50 threshold below 1,000 nM
- This epitope sequence is conserved in 94% of clade B isolates
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

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p24(131–152)	p24(263–284 SF2)	KRWIILGLNKIVRMYS-PTSILD	HIV-1 infection	human( )	[Rosenberg1997]

- Low viral load correlated with strong HIV-1-specific proliferative response
- A proliferative response to this epitope was detected in two long term survivors

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p24(135–154)	p24(267–286)	ILGLNKIVRMYSPTSIL-DIR	HIV-1 infection	human( )	[Adams1997]

- One of four immunogenic Gag peptides used in study of the proliferative response to p24
- 8/24 HIV+ individuals responded to this epitope
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) increased detection of proliferative response

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p24(141–156)	p24(273–287)	IVRMYSPTSILDIRQC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors
- Matches 3/3 anchor residues for HLA DR: **I**VRMY**S**PT**S**

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p24(146–160)	p24(278–292 IIIB B10)	SPTSILDIRQGPKEP	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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p24(150–169)	p24(282–301)	ILDIRQGPKEPFRDYV-DRFY	HIV-1 infection	human( )	[Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

p24(151–166)	p24(283–297)	LDIRQGPKEPFRDYVC	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors

p24(155–177)	p24(287–309)	QGPKEPFRDYVDRFY-KTLRAEQA	Vaccine	murine( )	[Nakamura1997a]

Vaccine: *Vector/type:* peptide

- Mice immunized with this peptide generated proliferative responses, CTLs and antibodies
- This immunogenic domain is from a highly conserved region of p24

p24(156–170)	p24(288–302 IIIB B10)	GPKEPFRDYVDRFYK	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

p24(156–174)	p24(287–306)	QPKEPFRDYVDRFYK-TLRA	HIV-1 infection	human( )	[Adams1997]

- One of four immunogenic Gag peptides used in study of the proliferative response to p24
- T-cells from 5/21 HIV+ individuals responded to this epitope
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) increased detection of proliferative response

p24(161–180)	p24(293–312 HXB2)	FRDYVDRFYKTLRAE-QASQD	Vaccine	murine(H-2^d, H-2^b)	[Mata1999]

Vaccine: *Vector/type: Listeria monocytogenes* *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways
- The class II T-helper response was probed using 20 mer peptides that overlapped by 10, and the peptides VHQAISPRTL-NAWVKVVEEK and FRDYVDRFYKTLRAEQASQD were recognized in H-2^b and H-2^d mice

p24(161–180)	Gag(293–312 SF2)	FRDYVDRFYKTLRAE-QASQD	Vaccine	murine(H-2d and H-2b)	[Mata1999]

Vaccine: *Vector/type:* Listeria moncytogenes *Strain:* SF2 *HIV component:* p24

- Listeria moncytogenes is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response
- Listeria moncytogenes vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T-cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice

- Two of three reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains – this peptide stimulated a response in both BALB/c and C57BL/6 mice
- The proliferative response is due to CD4+, IFN-γ producing cells, a Th1 response

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p24(163–177)	p24(295–309)	DYVDRFYKTLRAEQA	HIV-1 infection	human(DRB1*1302)	[Blankson2001, Malhotra2001]

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFNγ secretion and stronger proliferative responses against p24 80 weeks post-treatment
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay, and is highly conserved

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p24(181–196)	p24(313–327)	VKNWMTETLLVQNAN-C	*in vitro* stimulation	human( )	[Bedford1997a]

- Epitope elicits a primary proliferative response in PBMC from uninfected donors
- Matches 3/3 anchor residues for HLA DR: **V**KNWM**T**ET**L**

Table 3: **p2p7p1p6**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p2p7p1p6(30–44)	p15(393–407 IIIB B10)	FNCGKEGHTARNCRA	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses				
p2p7p1p6(55–69)	p15(418–432 IIIB B10)	KEGHQMKDCTERQAN	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses				
p2p7p1p6(60–74)	p15(423–437 IIIB B10)	MKDCTERQANFLGKI	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses				
p2p7p1p6(76–83)	p24(439–446 LAI)	PSYKGRPG	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors • Schrier lists this peptide as p24(439-446), but because of the numbering used for Gag epitopes, we placed it in p2p7p1p6				
p2p7p1p6(83–97)	p15(446–460 BRU)	GNFLQSRPEPTAPPA	*in vitro* stimulation	murine(H-2^b)	[Vaslin1994]
	• Epitope name: Peptide G4. could prime for *in vitro* immunoproliferative responses and for subsequent IgG responses				
p2p7p1p6(98–112)	p15(473–487 IIIB B10)	ESFRSGVETTTPPQK	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
	• Peptides were identified that commonly evoke T-cell responses – 50% of 90 HIV+ people had a T-cell response to this peptide				
p2p7p1p6(103–110)	p24(466–473 LAI)	REETTTPS	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors • Schrier lists this peptide as p24(466-473), but we placed it in p2p7p1p6				

Table 4: **Gag**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Gag( )	p24( )		HIV-1 infection, Vaccine	human( )	[Kelleher1998]

Vaccine: *Vector/type:* virus-like particle *HIV component:* p24, p17

- Immunization of HIV+ people with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre
- Immunization with p24-VLP showed a modest, short-lived increased proliferative response to p24

Gag( )	p24( )		HIV-1 infection, Vaccine	human( )	[Maino2000]

Vaccine: *Vector/type:* protein, gp120 depleted virus HZ321 (REMUNE^{TM}) *Strain:* Z321 *HIV component:* p24, gp120 depleted virus

- 18 HIV-1-seropositive patients with a low frequency or no detectable CD4+ T-cell response to HIV-1 antigen received an HIV-1 immunogen consisting of 10 units of native p24 and 100 ug of HZ321, a gp120 depleted antigen
- Using flow-cytometric methods, HIV-1 specific CD4+ T-cells were shown to increase in response to immunization – in many patients significant enhancement was observed after a single immunization
- The frequency of CD4+ T-cells expressing cytokines in response to antigen by FACS was correlated with a lymphoproliferation assay

Gag( )	p24( )		HIV-1 infection	human( )	[Ruiz2000]

- Structured treatment interruption in chronically infected patients allowed recovery of p24 Th proliferative responses after HAART therapy discontinuation in 2/12 patients
- The Th response to p24 was identified during peak viremia in one patient, while in the second it was noted when viremia was controlled after restarting antiviral therapy

Gag( )	p24( )		HIV-1 infection	human( )	[Lori1999]

- Ten patients with acute, pre-seroconversion HIV-1 infections were treated with didanosine, indinavir and hydroxyurea – this treatment is associated with normalization of immune parameters
- A vigorous HIV-specific Th response (stimulation index greater than 8) was observed in 7/8 patients treated before complete WB seroconversion, but in only 1/5 controls treated after seroconversion
- Vigorous Th responses were detected as early as 34 days after treatment begin
- Patients treated prior to seroconversion had no loss of naive CD4 T lymphocytes, recovery of up to 35% of the naive CD8 cells in several weeks, and a reduced latent viral reservoir

Gag( )	p24( )		HIV-1 infection	human( )	[Haslett2000]

- 11/22 adult patients on HAART showed strong CD4+ T-cell IFN-γ producing Th1 responses to HIV p24
- The magnitude of the Th1 response correlated with previous interruptions in HAART, suggesting the interruptions primed or boosted the response
- In contrast, the magnitude of the CD8+ CTL response did not correlate with interruptions in therapy, although a greater breadth in response was associated with interruptions in HAART

Gag( )	p24( )	HIV-1 infection, Vaccine	human( )	[Klein1996a]

Vaccine: *Vector/type:* virus-like particle *HIV component:* p24, p17

- Immunization of HIV+ people with a HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load
- Two of four subjects that received 500 or 1000 ug of p24-VLP had an increase in gag-specific CTL

Gag( )	p24( )	Vaccine	human( )	[Moss1998]

Vaccine: *Vector/type:* gp120 depleted virus HZ321 (REMUNE^{TM}) *Strain:* Z321 *HIV component:* gp120 depleted virus

- Immunization with gp120 depleted HZ321 virus (REMUNE^{TM}) triggered an increase in lymphocyte proliferative response to native p24, a clade B virus and clade E viral antigens – Z321 is clade A in env and clade G in gag. [Moss1998]

Gag( )	p24( )	HIV-1 infection	human( )	[Rosenberg1999]

- This paper reviews the role of T-cells in viral control and HIV disease outcome
- Strong anti-p24 lymphoproliferative responses were found in seven persons who were treated with potent anti-viral therapy during acute HIV-1 infection syndrome
- This suggests that Th cells are part of the normal response to HIV-1 infection, but their numbers are rapidly diminished by either being infected during the peak viremia or by activation-induced cell death – if peak viremia can be controlled, a robust anti-p24 Th response can be maintained

Gag( )	p24( )	HIV-1 infection	human( )	[Rosenberg1998]

- Strong Th responses have been found in rare individuals who effectively maintain low viral loads
- If aggressive anti-retroviral therapy is given prior to sero-conversion, strong helper responses can be maintained

Gag( )	p17( )	Vaccine	murine( )	[Birk1998a]

Vaccine: *Vector/type:* recombinant protein *HIV component:* p17

- Different p17 genes derived from the same quasispecies and expressed and purified in *E. coli* primed different Th1 and Th2 subsets in mice, depending on their H-2 type

Gag( )	Gag( )	HIV-1 infection	human( )	[Schiller2000]

- Study of parameters that might influence the performance or reproducibility of clinical Th proliferative assays
- HIV-1 replication *in vitro* is unlikely to influence the assay
- Gag proteins including p17 and possibly p7 as well as p24 perform better than p24 alone
- Frozen samples can be used in T-proliferative assays, but with lower radiolabled thymidine incorporation

Gag( )	Gag( )	HIV-1 infection	human( )	[Pitcher1999a]

- In contrast to earlier studies suggesting that HIV-1 specific Th responses were eliminated in the early stages of infection in most HIV+ individuals, this paper shows using flow cytometric detection of antigen-induced cytokines that Th1 CD4+ memory gag-specific Th cells are detectable in most HIV+ subjects

- Effective anti-viral therapy reduces the frequency of these cells, presumably due to reduced antigenic stimulus

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Gag( ) Gag( ) HIV-1 infection human( ) [Plana1998]

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses

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Gag( ) Gag( ) HIV-1 infection human( ) [Kelleher1998a]

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL-2 therapy – while IL-2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses

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Gag( ) Gag( ) Vaccine Macaca nemestrina( ) [Kent1998a]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *Strain:* LAI *HIV component:* Env, Gag

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env – The Th response happened despite a fall in Ab titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced

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Gag( ) ( ) Vaccine Rhesus macaque( ) [Heeney1999b]

Vaccine: *Vector/type:* DNA, protein, virus-like particle, ISCOM

- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge
- Protection correlated with the magnitude of NAb responses, β-chemokines, and a balanced Th response
- DNA, protein+adjuvant, VLP and ISCOM vaccines were tested
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced β-chemokine production

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Gag( ) Gag/Pol( ) Vaccine chimpanzee( ) [Kim1998d]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* Gag, Pol, Env *Stimulatory Agents:* CD80 and CD86 expression vectors

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Gag( ) Gag/Pol( ) Vaccine human( ) [Salmon-Ceron1999a]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers

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Gag( ) p55( ) HIV-1 infection human( ) [Zhang2001]

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient

- Untreated patients showed a negative correlation between plasma viral load and HIV p24-specific T-cell responses, and the responses could be detected after extended HAART therapy with viremia below the detection limit

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Gag( ) p24( ) HIV-1 infection human( ) [Carcelain2001]

- Repeated structured HAART therapy interruptions (STI) in 3 chronically HIV infected patients induced rapid but transient (< 3 weeks) HIV-1 specific CD4+ Th1 responses concurrently with viral rebound, as measured by proliferation assays and by IFNγ production by CD8-depleted PBMC
- Kinetics suggest that viral replication leads to rapid destruction of the HIV-specific Th1 cell response
- HIV-specific CD8+ T-cell responses were delayed relative to the Th1 responses and were not sustained

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Gag( ) Gag( ) HIV-1 infection human( ) [Blankson2001a]

- 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy experienced immune reconstitution, and displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment
- This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T-cells

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Gag( ) p24( ) HIV-1 infection human( ) [Angel2001]

- Prolonged viral suppression resulting from potent anti-retroviral therapy allowed a T-helper response to Gag p24 and PHA to develop in many HIV+ patients
- At baseline, 2/41 (4.9%) subjects had a proliferative response to Gag p24, and 7/41 (17.1%) had a response to PHA, but by week 72 of therapy, 53% had a detectable response to p24 and 94% to PHA

Gag( ) p24( ) HIV-1 infection human( ) [Blazevic2000]

- Prolonged viral suppression resulting from potent anti-retroviral therapy did not allow an HIV T-helper response increase to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients

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Gag( ) Gag( ) HIV-1 infection human( ) [Altfeld2001b]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T-helper response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the CTL response was determined using Elispot by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Individuals who were given HAART during acute or early in infection had significantly stronger proliferative responses than individuals who were chronically infected

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Gag( ) p24( ) HIV-1 infection human( ) [Oxenius2000b]

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable

- In 3/4 responders tested p24 gave the strongest T-helper response

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Gag( ) p24( ) Vaccine rat( ) [Moss2001]

Vaccine: *Vector/type:* gp120 depleted whole killed virus *Strain:* HZ321 (subtype A env, subtype G gag) *HIV component:* whole virus *Stimulatory Agents:* CpG, Freund's adjuvant

- Lewis rats simultaneously immunized with HIV-1 antigen and with immunostimulatory sequences CpG had increased Th proliferative responses, but when CpG was given as a prime prior to the injection of HIV-1 antigen it was not as effective

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Gag( ) p24( ) Vaccine rat( ) [Moss2000]

Vaccine: *Vector/type:* gp120 depleted whole killed virus *Strain:* HZ321 (subtype A env, subtype G gag) *HIV component:* whole virus *Stimulatory Agents:* CpG, Freund's adjuvant

- Lewis rats co-immunized with HIV-1 antigen in Freund's and with immunostimulatory sequences CpG stimulated increased IFNγ expressing CD4+ and CD8+ T-cells and anti-p24 antibodies relative to antigen in Freund's without CpG

Gag( ) p24( ) *in vitro* stimulation human(A*0201) [Engelmayer2001]

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific IFNγ CD4+ helper T-cell responses to Gag from bulk or purified CD4+ T-cells

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Gag( ) p24( ) Vaccine murine(H-2^d) [Qiu2000a]

Vaccine: *Vector/type:* DNA *HIV component:* Gag

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors
- IFN-γ levels were increased compared to an undetectable IL-4 response
- CTL levels were also increased in secreted Gag expression vaccination studies

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Gag( ) Gag( ) Vaccine murine(H-2^d) [BillautMulot2001]

Vaccine: *Vector/type:* DNA with DNA boost, DNA with recombinant protein boost *Strain:* LAI *HIV component:* Gag, Tat, Nef *Stimulatory Agents:* IL-18

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL-18 showed lymphoproliferative responses 7 weeks post immunization
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFNγ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable
- Co-administration of IL-18 increased T-cell responses but decreased anti-HIV antibody levels

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Gag( )	p24( )		Vaccine	murine(H-2^d)	[Halim2000]

Vaccine: *Vector/type:* coxsackievirus *HIV component:* partial p24, polyepitope

- An avirulent rec coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T-helper responses can be elicited from peptides embedded in a surface loop of the VP1 capsid
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice

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Gag( )	Gag( )	none	Vaccine	murine(H-2^d, H-2^b)	[Mata2001]

Vaccine: *Vector/type: Listeria monocytogenes* *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag
- Gag-specific CTL may enhance viral clearance via IFNγ secretion, but are not essential for immunity

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Gag( )	Gag( )	none	Vaccine	murine(H-2^d, H-2^b)	[Mata2000]

Vaccine: *Vector/type: Listeria monocytogenes* *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways
- This article is a review of *L. monocytogenes* biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cells mediated Gag specific immunological protection in mice and the Gag CTL response

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Table 5: **RT**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
RT(36–52)	RT(36–52 BRU)	EICTEMEKEGKISKIGP	HIV-1 infection	human( )	[DeGroot1991a]
	• 9 out of 17 humans can make strong IL-2 responses to this epitope				
RT(38–52)	RT(38–52 BRU)	CTEMEKEGKISKIGP	Vaccine	murine(H-2^k)	[DeGroot1991a]
	Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT				
	• T-cells from RT immunized mice have enhanced proliferative response with peptide				
RT(39–53)	RT(194–208)	TEMEKEGKISKIGPE	*in vitro* stimulation	human( )	[Manca1995c]
	• Protein priming induced T-cells that recognize peptide, 4 clones from a single donor recognized this peptide				
RT(48–62)	RT(48–62 BRU)	SKIGPENPYNTPVFA	Vaccine	murine(H-2^k)	[DeGroot1991a]
	Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT				
	• T-cells from RT immunized mice have enhanced proliferative response with peptide				
RT(62–77)	RT(62–77 BRU)	AIKKKDSTKWRKLVDF	Vaccine	murine(H-2^k)	[DeGroot1991a]
	Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT				
	• T-cells from RT immunized mice have enhanced proliferative response with peptide				
RT(88–102)	RT(88–102 BRU)	WEVQLGIPHPAGLKK	Vaccine	murine(H-2^{t4})	[DeGroot1991a]
	Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT				
	• T-cells from RT immunized mice have enhanced proliferative response with peptide				
RT(124–138)	Pol(303–317)	FRKYTAFTIPSINNE	HIV-1 infection	human(DR supermotif)	[Wilson2001]
	• Epitope name: Pol 303. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors				
	• This epitope binds seven HLA-DR alleles: DRB1*0901, DRB1*0802, DRB1*0701, DRB1*0405, DRB1*0401, DRB1*1501 and DRB1*0101, with an IC50 threshold below 1,000 nM				
	• This epitope sequence is conserved in 68% of clade B isolates				
	• 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)				
RT(133–147)	RT(133–147 BRU)	PSINNETPGIRYQYN	Vaccine	murine(H-$2^{k,i5}$)	[DeGroot1991a]
	Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT				
	• T-cells from RT immunized mice have enhanced proliferative response with peptide				

RT(144–158)	RT(144–158 BRU)	YQYNVLPQGWKGSPA	Vaccine	murine(H-2^{t4})	[DeGroot1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT

- T-cells from RT immunized mice have enhanced proliferative response with peptide

RT(156–170)	Pol(335–349)	SPAIFQSSMTKILEP	HIV-1 infection	human(DR supermotif)	[Wilson2001]

- Epitope name: Pol 596. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors
- This epitope binds nine HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0901, DRB5*0101 and DRB3*0101, with an IC50 threshold below 1,000 nM
- This epitope sequence is conserved in 79% of clade B isolates
- 7/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

RT(171–190)	RT(171–190 HXB2)	FRKQNPDIVIYQYMD-DLYVG	HIV-1 infection	human(DR1, 2 or 3, 4 and 7)	[vanderBurg1999]

- T-cells specific for this epitope from the three donors were stimulated when presented with target cells pulsed with whole RT, indicating that the peptide is naturally processed for multiple HLA-DR molecules
- Epitope binds to HLA-DR1, -DR2, -DR3, -DR4, and DR7, and can elicit Th1 cells that recognize peptide, protein, and HIV pulsed stimulator cells in the context of DR1, 2 or 3, 4 and 7 – these HLA types cover more than half of the general population

RT(195–209)	RT( )	IGQHRTKIEELRQHL	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(196–215)	RT(351–370)	GQHRTKIEELRQHLLR-WGLT	*in vitro* stimulation	human( )	[Manca1995c]

- Protein priming induced T-cells that recognize peptide, 4 clones from a single donor recognized this peptide

RT(249–263)	RT( )	KDSWTWNDIQKLVGK	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming did not induce T-cells that recognize whole protein

RT(249–263)	RT(248–262)	KDSWTVNDIQKLVGK	*in vitro* stimulation	human( )	[DeBerardinis1999]

- PBMC from donors GD (HLA DR 11; DRB52) and LD (HLA DR 11, 13; DRB52) recognized this epitope (pep23)
- A subset of T-cell lines generated from these donors were capable of recognizing pep23 expressed on the surface of filamentous phage fd, fused to the major coat protein gVIIIp
- This peptide was selected to study phage presentation of peptide sequences because it was known to serve as a T-cell helper determinant which could induce proliferation from a naive repertoire [Manca1995a]

RT(249–263)	RT(249–263)	KDSWTVNDIQKLVGK	Vaccine, *in vitro* stimulation	human(DR5)	[DeBerardinis2000]

Vaccine: *Vector/type:* HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT peptides

- Epitope name: RT2. Phage display of the CTL epitope, ILKEPVHGV coupled with T-helper epitope KDSWTVNDIQKLVGK, elicited specific CTL responses in PBMC from HIV negative individuals and *in vivo* in immunization of HLA-A2 transgenic mice
- Bacteriophage presentation of peptides is generally used for stimulation of antibodies, and this novel discovery of CTL epitope processing and presentation suggests new possibilities for these vectors
- HIV-1 peptides were displayed in filamentous bacteriophage fd virion major coat protein pVIII

RT(249–263)	RT(248–262 HXB2)	KDSSTVNDIQKLVGK	*in vitro* stimulation	human(DRS)	[Fenoglio1999]

- RT pep23 epitope exhibited antagonistic activity against proliferation of gp120-specific T-cells when flanked by unrelated amino acid sequence
- The glutathione S-transferase (GST)-peptide system can be used to display peptides; antigenicity was maintained when this peptide was expressed at the C-term end, but antagonism resulted when this peptide was expressed at the N-term end

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RT(251–261)	RT(250–260)	SSTVNDIQKLV	*in vitro* stimulation	human(DR5(11.01))	[Manca1996]

- This peptide was the minimal stimulatory sequence
- One Th line was stimulated by p66, one by a Glutathione-S-transferase (GST)-peptide fusion protein
- Constructs linking GST to the KDSSTVNDIQKLVGK peptide at the N-term end of GST stimulated Th cells, but not constructs linking at the C-term end
- The C and N termini of GST are not intrinsically permissive or non-permissive, presentation is epitope specific (see FAILKCNNK for contrast)

RT(258–272)	RT( )	QKLWGKLNWASQIYP	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming did not induce T-cells that recognize whole protein

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RT(271–290)	RT(271–290 HXB2)	YPGIKVRQLCKLLRGT-KALT	HIV-1 infection	human( )	[vanderBurg1999]

- Epitope can bind to at least 5 different HLA-DR molecules, and peptide on target cells can elicit Th responses from PBMC cultures from healthy donors, however it does not seem to be processed properly from whole RT or virus

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RT(276–290)	RT( )	WRQLCKLLRGTKALT	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(285–299)	RT( )	GTKALTEVIPLTEEA	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(294–308)	RT( )	PLTEEAELELAENRE	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(303–317)	RT( )	LAENREILKEPVHGV	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(384–398)	RT( )	GKTPKFKLPIQKETW	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(414–428)	Pol(596–610)	WEFVNTPPLVKLWYQ	HIV-1 infection	human(DR supermotif)	[Wilson2001]

- Epitope name: Pol 596. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors
- This epitope binds eleven HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101, with an IC50 threshold below 1,000 nM
- This epitope sequence is conserved in 84% of clade B isolates
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

RT(429–443)	RT( )	LEKEPIVGAETFYVD	*in vitro* stimulation	human( )	[Manca1995b]

- Protein priming induced T-cells that recognize peptide

RT(528–543)	RT(528–543 BRU)	KEKVYLAWVPAHKGI-G	Vaccine	murine(H-$2^{f,k,d}$)	[Haas1991]

Vaccine: *Vector/type:* peptide *Strain:* BRU

- T-cells from peptide-primed mice could be restimulated by native RT

RT(529–543)	Pol(711–725)	EKVYLAWVPAHKGIG	HIV-1 infection	human(DR supermotif)	[Wilson2001]

- Epitope name: Pol 711. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors
- This epitope binds ten HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101, with an IC50 threshold below 1,000 nM
- This epitope sequence is conserved in 94% of clade B isolates
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

RT(530–544)	Pol(712–726)	KVYLAWVPAHKGIGG	HIV-1 infection	human(DR supermotif)	[Wilson2001]

- Epitope name: Pol 712. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors
- This epitope binds ten HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101, with an IC50 threshold below 1,000 nM

	• This epitope sequence is conserved in 89% of clade B isolates • 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)				
RT(553–560)	RT(720–730 LAI)	SAGIRKVLFLD	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors				

Table 6: **Integrase**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Integrase(16–30)	Pol(758–772)	HSNWRAMASDFNLPP	HIV-1 infection	human(DR supermotif)	[Wilson2001]
	• Epitope name: Pol 758. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors • This epitope binds eight HLA-DR alleles: DRB4*0101, DRB5*0101, DRB1*0901, DRB1*0701, DRB1*1101, DRB1*0405, DRB1*0401 and DRB1*0101, with an IC50 threshold below 1,000 nM • This epitope sequence is conserved in 68% of clade B isolates • 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)				
Integrase(172–186)	RT(899–913 LAI)	LKTAVQMAVFIHNFK	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors				
Integrase(173–187)	Pol(915–929)	KTAVQMAVFFIHNFKR	HIV-1 infection	human(DR supermotif)	[Wilson2001]
	• Epitope name: Pol 915. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors • This epitope binds seven HLA-DR alleles: DRB5*0101, DRB1*1302, DRB1*1101, DRB1*0405, DRB1*0401, DRB1*1501 and DRB1*0101, with an IC50 threshold below 1,000 nM • This epitope sequence is conserved in 94% of clade B isolates • 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)				
Integrase(196–210)	RT(923–937 LAI)	AGERIVDIIATDIQT	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors				
Integrase(214–228)	Pol(956–970)	QKQITKIQNFRVYYR	HIV-1 infection	human(DR supermotif)	[Wilson2001]
	• Epitope name: Pol 956. Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors • This epitope binds twelve HLA-DR alleles: DRB4*0101, DRB5*0101, DRB1*0901, DRB1*0802, DRB1*0701, DRB1*1302, DRB1*1201, DRB1*1101, DRB1*0405, DRB1*0401, DRB1*1501 and DRB1*0101, with an IC50 threshold below 1,000 nM • This epitope sequence is conserved in 95% of clade B isolates • 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)				

Integrase(215–227)	RT(942–954 LAI)	KQITKIQNFRVYY	HIV-1 infection	human( )	[Schrier1989]
	• Stimulates T-cell proliferation in HIV-infected donors				

Table 7: **Pol**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Pol( )	Gag/Pol( )		Vaccine	murine( )	[Kim1997e]
Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, VIF *Stimulatory Agents:* B7 and IL-12 expression vector					
• A gag/pol DNA vaccine delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12 gives a dramatic increase in both the cytotoxic and proliferative responses in mice					
Pol( )	Gag/Pol( )		Vaccine	murine( )	[Kim1997f]
Vaccine: *Vector/type:* DNA *HIV component:* gp160, Gag, Pol *Stimulatory Agents:* CD86 expression vectors					
• A gag/pol DNA vaccine delivered in conjunction with the plasmid encoding the co-stimulatory molecule CD86 gives an increase in proliferative responses to Pr55 in mice					
Pol( )	Gag/Pol( )		Vaccine	chimpanzee( )	[Kim1998d]
Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* Gag, Pol, Env *Stimulatory Agents:* CD80 and CD86 expression vectors					
• Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses					
Pol( )	Pol( )		HIV-1 infection	human( )	[Blankson2001a]
• 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy experienced immune reconstitution, and displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment					
• This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T-cells					
Pol( )	p66( )		HIV-1 infection	human( )	[Oxenius2000b]
• Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable					
Pol( )	RT(248–256 HXB2)		*in vitro* stimulation	human(DR5)	[Manca1995b]
• CD4+ T-cell lines from uninfected individuals by stimulation with p66-pulsed APC					
• TcR Vβ Dβ Jβ sequences were obtained from p66-specific T-cell clones					
• There were multiple responses to peptides throughout p66					
• Response to peptide 248-256 was associated with DR5					

Pol( )	RT( )	Vaccine	murine(H-2^d)	[Kim2000a]

Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Env *Stimulatory Agents:* IL-2, IL-4 and IFNγ expression vectors

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of Th1 cytokine IFN-γ drove Th1 immune responses and enhanced CTL responses

Pol( )	RT( )	Vaccine	murine(H-2^d)	[Burnett2000]

Vaccine: *Vector/type:* Salmonella *HIV component:* RT epitope

- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV RT gene in the Lpp-OmpA-HIV fusion protein, induced a lymphoproliferative Th response in BALB/c mice

Table 8: **Vif**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Vif(65–76)	Vif(65–80)	VITTYWGLHTGE	HIV-1 infection	human( )	[Ranki1997]
	• T-cell response to this epitope persisted after seroreversion				
Vif(81–96)	Vif(81–96)	LGQGVSIEWRKQRYST	HIV-1 infection	human( )	[Ranki1997]
	• T-cell response to this epitope persisted after seroreversion				
Vif( )	Vif( )		Vaccine	murine(H-2^d)	[Ayyavoo2000a]
	Vaccine: *Vector/type:* DNA *HIV component:* Vif, Vpu, Nef				
	• Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels				
	• Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response				
	• IL-4 production was not significantly changed after antigen stimulation compared to control levels				
	• Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell				

Table 9: **Vpr**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Vpr(66–80)	vpr(66–80 IIIB)	QLLFIHFRIGCRHSR	HIV-1 infection	human( )	[Sarobe1994]
	• This peptide was found to stimulate proliferative responses in 37.5% of HIV-1 positive individuals				
Vpr(66–80)	vpr(66–80 IIIB)	QLLFIHFRIGCRHSR	Vaccine	murine(H-2^d)	[Sarobe1994]
	Vaccine: *Vector/type:* peptide				
	• Included as a Th stimulatory component of peptide vaccines that also incorporated B-cell epitopes				

Table 10: **Tat**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Tat(1–20)	Tat(1–20 LAI)	MEPVDPRLEPWKHPG-SQPKT	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Tat(16–35)	Tat(16–35 LAI)	SQPKTACTTCYCKKC-CFHCQ	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Tat(17–32)	Tat(17–32)	QPKTACTNCYCKRCCF	HIV-1 infection	human( )	[Ranki1997]
• T-cell response to this epitope persisted after seroreversion					
Tat(31–50)	Tat(31–50 LAI)	CFHCQVCFTTKALGIS-YGRK	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Tat(33–48)	Tat(33–48)	HCQVCFMTKGLGISYG	HIV-1 infection	human( )	[Ranki1997]
• T-cell response to this epitope persisted after seroreversion					
Tat(46–65)	Tat(46–65 LAI)	SYGRKKRRQRRRPPQ-GSQTH	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Tat(61–80)	Tat(61–80 LAI)	GSQTHQVSLSKQPTSQ-PRGD	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally; rather than with intramuscular protein					

- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Tat(67–86)	Tat(67–86 LAI)	VSLSKQPTSQPRGDPT-GPKE	Vaccine	murine(H-2^d)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Tat( )	Tat( )	Vaccine	human( )	[Calarota1999a]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Tat, Rev

- Nine HIV-1+ subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination

Tat( )	Tat( )	HIV-1 infection, Vaccine	human( )	[Calarota2001]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev, Tat *Stimulatory Agents:* CpG motifs

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals

Tat( )	Tat( )	Vaccine	murine(H-2^d)	[BillautMulot2001]

Vaccine: *Vector/type:* DNA with DNA boost, DNA with recombinant protein boost *Strain:* LAI *HIV component:* Gag, Tat, Nef *Stimulatory Agents:* IL-18

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL-18 gave lymphoproliferative responses 7 weeks post immunization
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFNγ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable
- Co-administration of IL-18 increased T-cell responses but decreased anti-HIV antibody levels

Table 11: **Rev**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Rev(9–23)	Rev(9–23 HXB2)	DEELIRTVRLIKLLY	HIV-1 infection	human( )	[Blazevic1995a]
• One of four peptides that stimulates in PBLs from HIV-1+ donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide					
Rev(16–35)	Rev(16–35 LAI)	VRLIKFLYQSNPPPNPE-GTR	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev					
• Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein					
• Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Rev(25–39)	Rev(25–39 HXB2)	SNPPPNPEGTRQARR	HIV-1 infection	human( )	[Blazevic1995a]
• One of four peptides that stimulates in PBLs from HIV-1+ donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide					
Rev(31–50)	Rev(31–50 LAI)	PEGTRQARRNRRRRW-RERQR	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev					
• Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein					
• Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Rev(33–48)	Rev(33–48 HXB2)	GTRQARRNRRRRWRE-R	HIV-1 infection	human( )	[Blazevic1995a]
• One of four peptides that stimulates in PBLs from HIV-1+ donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide					
Rev(41–56)	Rev(41–56 HXB2)	RRRRWRERQRQIHSIS	HIV-1 infection	human( )	[Blazevic1995a]
• One of four peptides that stimulates in PBLs from HIV-1+ donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide					
Rev(76–95)	Rev(76–95 LAI)	PPLERLTLDCNEDCGT-SGTQ	Vaccine	murine(H-2^b)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev					
• Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein					
• Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					

Rev(96–116)	Rev(96–116 LAI)	GVGSPQILVESPTVLES-GTKE	Vaccine	murine(H-2^d)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

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Rev( )	Rev( )	Vaccine	murine( )	[Chan1998]

Vaccine: *Vector/type:* DNA *HIV component:* Rev

- Rev M10 is a construct that was introduced into mice through a genetic vaccination
- Rev was used to test for down-regulation of HIV-1 in infected cells as a method for gene therapy – in the course of this study, Rev-specific IL-2 producing Th cells developed in the mice

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Rev( )	Rev( )	Vaccine	human( )	[Calarota1999a]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev Tat

- Nine HIV-1+ subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination

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Rev( )	Rev( )	HIV-1 infection, Vaccine	human( )	[Calarota2001]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev, Tat *Stimulatory Agents:* CpG motifs

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals

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Table 12: **Vpu**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Vpu(19–34)	Vpu(19–34)	AIVVWSIVLIEYRKIL	HIV-1 infection	human( )	[Ranki1997]
	• T-cell response to this epitope persisted after seroreversion				
Vpu( )	Vpu( )		Vaccine	murine(H-2^d)	[Ayyavoo2000a]
	Vaccine: *Vector/type:* DNA *HIV component:* Vif, Vpu, Nef				
	• Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels				
	• Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response				
	• IL-4 production was not significantly changed after antigen stimulation compared to control levels				
	• Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell				

Table 13: **gp160**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
gp160(32–44)	gp120(39–51)	EQLWVTVYYGVPV	Vaccine	murine(H-2^{bxk})	[Sastry1991]
Vaccine: *Vector/type:* peptide					
• Peptides induced T-cell proliferative response to immunizing peptide and to gp160					
gp160(38–48)	Env(45–55)	VYYGVPVWKEA	Vaccine	Rhesus macaque( )	[Nehete1993]
Vaccine: *Vector/type:* peptide					
• Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice • Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys					
gp160(38–48)	Env(45–55)	VYYGVPVWKEA	HIV-1 infection	human, chimpanzee( )	[Nehete1998a]
• 7/9 HIV-infected chimpanzees and 8/17 HIV-positive humans exhibited positive proliferative responses to this conserved peptide (peptide 104) – no HIV negative individuals showed a response • This peptide, along with 4 other peptides from conserved regions of envelope, can induce proliferative responses to HIV and may be useful for vaccines • Peptide 104 elicited proliferative responses in inbred mouse strains and outbred rhesus monkeys in previous study by same group					
gp160(38–48)	gp120(45–55)	VYYGVPVWKEA	Vaccine	murine(H-$2^{bxk,sxd}$)	[Sastry1991]
Vaccine: *Vector/type:* peptide					
• Peptides induced T-cell proliferative response to immunizing peptide and to gp160					
gp160(41–54)	Env(48–60)	GVPVWKEATTLFC	Vaccine	Rhesus macaque( )	[Nehete1993]
Vaccine: *Vector/type:* peptide					
• Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice • Despite the proliferative response to this peptide in mice, no response was observed in 3 rhesus monkeys					
gp160(41–54)	gp120(48–61)	GVPVWKEATTLFC	Vaccine	murine(H-2^{sxd})	[Sastry1991]
Vaccine: *Vector/type:* peptide					
• Peptides induced T-cell proliferative response to immunizing peptide and to gp160					
gp160(41–60)	gp120(40–59 89.6)	GVPVWREATTTLFCA-SDAKA	Vaccine	murine(H-2^{d})	[Dai2001]
Vaccine: *Vector/type:* recombinant protein *Strain:* 89.6 *HIV component:* gp120 *Stimulatory Agents:* mutant R192G heat-labile toxin from *E. coli* as adjuvant					

- Promiscuous immunodominant epitope in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence
- This peptide was recognized by 10/10 BALB/c with an average SI of 6.4, the strongest reaction among BALB/c mice, but not by CBA/J mice, but recognized well not by CBA/J mice, so is considered to be uniquely immunodominant for H-2^d
- Uniquely immunodominant sequences tended to be in the interior of the protein

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gp160(65–75) | gp120(72–82) | AHKVWATHACV | Vaccine | murine(H-2^{bxk,sxd}) | [Sastry1991]

Vaccine: *Vector/type:* peptide

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160

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gp160(74–85) | gp120(74–85 LAI) | CVPTDPNPQEVV | HIV-1 infection | human( ) | [Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

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gp160(74–85) | gp120(81–92) | CVPTNPVPQEVV | Vaccine | murine(H-2^{bxk,sxd}) | [Sastry1991]

Vaccine: *Vector/type:* peptide

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160

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gp160(80–99) | gp120(51–70 HXB2) | NPQEVVLVNTENFNM-WKND | *in vitro* stimulation | human( ) | [LiPira1998]

- Clonal heterogeneity was broad for a recall response to tetanus toxoid or PPD, but oligoclonal to primary HIV antigens, dominated in this case by TCR Vβ 13 usage
- Donor of PBMC that recognized this epitope had HLA-DR2 and HLA-DR7

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gp160(81–100) | gp120(80–99 89.6) | PQEVVLGNVTENFNM-WKNNM | Vaccine | murine(H-2^k) | [Dai2001]

Vaccine: *Vector/type:* recombinant protein *Strain:* 89.6 *HIV component:* gp120 *Stimulatory Agents:* mutant R192G heat-labile toxin from *E. coli* as adjuvant

- Promiscuous immunodominant epitope in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence
- This peptide was recognized by 10/10 CBA/J mice with an average SI of 8.2, but not by BALB/c mice, so is considered to be uniquely immunodominant for H-2^k
- Uniquely immunodominant sequences tended to be in the interior of the protein

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gp160(92–101) | gp120(90–100 W6.ID) | YFNMWKNNMV | Vaccine | human( ) | [Jones1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* W61D *HIV component:* gp120 *Stimulatory Agents:* QS21/MPL adjuvant

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated
- One T-cell clone reacts with two overlapping peptides, and the region of overlap is: YFNMWKNNMV
- The first 20-mer peptide that this clone reacts with is PQEVVLGNVTEYFNMWKNNMV, and the IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version: IIIB: `------V----N-D----D--`

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gp160(92–111)	gp120(92–111 W6.ID)	YFNMWKNNMVDQMHE-Vaccine DIISL		human( )	[Jones1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* W61D *HIV component:* gp120 *Stimulatory Agents:* QS21/MPL adjuvant

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide `N-D----D--E---------`
- Six T-cell lines react with this peptide, but some of these can also be stimulated by other gp120 peptides located in different regions of gp120

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gp160(101–126)	gp120(101–126)	VEQMHEDIISLWDQSL-KPCVKLTPLC	Vaccine	murine(H-2^k)	[Sjolander1996]

Vaccine: *Vector/type:* recombinant protein *HIV component:* gp160

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein

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gp160(102–114)	gp120(109–121)	EQMHEDIISLWDQ	Vaccine	murine(H-2^{bxk})	[Sastry1991]

Vaccine: *Vector/type:* peptide

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160

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gp160(102–116)	gp160(109–123 IIIB)	EQMHEDIISLWDQSL	Vaccine	murine(H-2^d, H-2^b)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- B10.D2 (H-$2A^d$, E^d) and B10.A(R5) (H-$2A^b$, E^b) mice immunized with rec gp160 showed a proliferative response to EQMHEDIISLWDQSL
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes including HEDIISLWDQSLK and is referred to as a "multideterminant region" or cluster peptide

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gp160(102–116)	gp120(109–123 IIIB)	EQMHEDIISLWDQSL	Vaccine	murine(H-$2^{d,i5}$)	[Hale1989]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(102–121)	gp160(109–128 IIIB)	EQMHEDIISLWDQSLK-PCVK	HIV-1 infection, Vaccine	human, murine(H-2^k, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people
- This cluster peptide elicited proliferative responses in cells from vaccinated B10.BR mice (H-2A^k, E^k) and B10.S(9R) mice (H-2A^s, E^s), while shorter peptides from within this region stimulated H-2^k, H-2^d and H-2^b responses, but not H-2^s
- IL-2 production was observed in response to this peptide in 64% (23/36) of asymptomatic HIV-infected individuals

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 infection	human( )	[Clerici1997]

- Epitope name: T2. Used in a study of pentoxifylline's influence on HIV specific T-cells

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gp160(105–117)	gp120(112–124 BH10)	HEDIISLWDQSLK	Vaccine	human( )	[Berzofsky1988]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: T2. Proliferative response to T1 and T2 peptides in 14 immunized, uninfected humans

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 infection	human( )	[Clerici1989]

- Epitope name: T2. IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 infection	human( )	[Clerici1991a]

- Epitope name: T2. Peptides stimulate Th cell function and CTL activity in similar patient populations

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gp160(105–117)	gp120(112–124)	HEDIISLWDQSLK	Vaccine	human( )	[Clerici1991b]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160

- Epitope name: T2. Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 exposed seronegative	human( )	[Clerici1992]

- Epitope name: T2. Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	Vaccine	Rhesus macaque( )	[Hosmalin1991]

Vaccine: *Vector/type:* peptide prime with protein boost *Strain:* IIIB *HIV component:* gp160

- Epitope name: T2. Peptide priming to induce T-cell help enhances antibody response to gp160 immunization

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 exposed seronegative	human( )	[Pinto1995a]

- Epitope name: T2. CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 exposed seronegative	human( )	[Kaul1999a]

- Epitope name: T2. Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- The helper epitopes used in this study were noted to be previously described [Clerici1989], and were not explicitly described in [Kaul1999a]

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gp160(105–117)	gp120( )	HEDIISLWDQSLK	HIV-1 exposed seronegative, HIV-1 infection	human( )	[Kuhn2001]

- Epitope name: T2. In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL-2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4
- The mothers were predominantly infected subtype C but the T-helper response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents
- 3/33 infants with cord blood T-helper responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected – 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding
- Measurable HIV specific T-helper responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1

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gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	Vaccine	murine(H-2^k)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Epitope name: T2. Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(105–117)	gp160(112–124 IIIB)	HEDIISLWDQSLK	Vaccine	murine(H-2^k)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- B10.BR (H-2A^k, E^k) mice immunized with rec gp160 showed a strong proliferative response to three overlapping peptides, QMHEDIISLWDQSL, HEDIISLWDQSLK, and DIISLWDQSLKPCVK, and HEDIISLWDQSLK is common to between them
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes including HEDIISLWDQSLK and is referred to as a "multideterminant region" or cluster peptide

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gp160(105–117)	gp120(112–124 BH10)	HEDIISLWDQSLK	computer prediction	murine(H-$2^{k,s}$)	[Cease1987a]

- Epitope name: T2. 1 of 2 functional epitopes identified using an amphipathic helix epitope prediction algorithm

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gp160(105–123)	gp120(112–130 IIIB)	HEDIISLWDQSLKPCV-KLT		human( )	[Furci1997]

- 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but none reacted with this previously defined epitope

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gp160(108–119) gp120(108–119 LAI) IISLWDQSLKPC HIV-1 infection human( ) [Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

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gp160(110–125) gp120(110–125) SLWDQSLKPCVKLTPL HIV-1 infection human( ) [Caruso1997]

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24

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gp160(111–123) gp120(118–130) LWDQSLKPCVKLT Vaccine Rhesus macaque( ) [Nehete1993]

Vaccine: *Vector/type:* peptide

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice
- Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys

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gp160(112–141) gp120(112–141 NL43) WDQSLKPCVKLTPLC-VSLKCTDLGNATNTN Vaccine human( ) [Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients
- Over 35% of vaccinees had a stimulation index of greater than 5 to this peptide

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gp160(115–126) gp120(115–126 LAI) SLKPCVKLTPLC HIV-1 infection human( ) [Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

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gp160(115–129) gp120(115–129 LAI) SLKPCVKLTPLCVSL Peptide-HLA interaction human(HLA-DR) [Gaudebout1997]

- Peptide bound to both HLA-DR*1101 and HLA-DR*0401 with high affinity
- Because of the distinctive binding pockets of HLA-DR*1101 and HLA-DR*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding

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gp160(138–159) gp120(141–160 W6.ID) TTSNGWTGEIRKGEIK-NCSF Vaccine human( ) [Jones1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* W61D *HIV component:* gp120 *Stimulatory Agents:* QS21/MPL adjuvant

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide: IIIB: `---SSGRMIME---------`

gp160(147–168)	gp120(152–173 NL43)	MMMEKGEIKNCSFNI-STSIRGK	Vaccine	human( )	[Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients
- Over 50% of vaccinees had a stimulation index of greater than 5 to this peptide

gp160(155–169)	Env( )	KNCSFNITTELIDKK	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V2 region of UG92005 (UG, clade D) and the hybridoma that recognized it used Vβ5
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

gp160(155–169)	gp120(160–174 LAI)	KNCSFNISTSIRGKV		human(HLA-DR)	[Gaudebout1997]

- Peptide binds to both HLA-DR*1101 and HLA-DR*0401 with high affinity
- Because of the distinctive binding pockets of HLA-DR*1101 and HLA-DR*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding

gp160(162–181)	gp120(162–181 IIIB)	STSIRGKVQKEYAFFY-KLDI	Vaccine	Rhesus macaque( )	[Lekutis1997a]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* Env

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkeys

gp160(169–189)	gp120(141–160 W6.ID)	VQKEYALFYNLDVVPI-DDDNA	Vaccine	human( )	[Jones1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* W61D *HIV component:* gp120 *Stimulatory Agents:* QS21/MPL adjuvant

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide `------F--K--II---N-TT`
- Two T-cell lines react specifically with this peptide

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gp160(172–191)	gp120(172–191 IIIB)	EYAFFYKLDIIPIDNDT-TSY	Vaccine	Rhesus macaque( )	[Lekutis1997a]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* Env

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkey

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gp160(175–189)	Env( )	LFYKLDVVQIDNSTN	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V2 region of UG92005 (UG, clade D) and the Vβ usage of the TCR was not determined
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(185–215)	gp120(191–220 NL43)	NDTTSYTLTSCNTSVIT-QACPKVSFEPIPI	Vaccine	human( )	[Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients

- Over 30% of vaccinees had a stimulation index of greater than 5 to this peptide

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gp160(188–207) | gp120(190–209 89.6) | NTKYRLISCNTSVITQ-ACPK | Vaccine | murine(H-2^k) | [Dai2001]

Vaccine: *Vector/type:* recombinant protein *Strain:* 89.6 *HIV component:* gp120 *Stimulatory Agents:* mutant R192G heat-labile toxin from *E. coli* as adjuvant

- Promiscuous immunodominant epitope in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence
- This peptide was recognized by 9/10 CBA/J mice with an average SI of 9.8, one of the two immunodominant peptides in CBA/J mice, and not by BALB/c mice, so is considered to be uniquely immunodominant for H-2^k
- Uniquely immunodominant sequences tended to be in the interior of the protein

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gp160(193–218) | gp120(193–218) | LTSCNSVITQACPKVS-FEPIPIHYC | Vaccine | murine(H-2^{d,b}) | [Sjolander1996]

Vaccine: *Vector/type:* recombinant protein *HIV component:* gp160

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein

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gp160(198–212) | Env( ) | TSVITQACPKVSFEP | Vaccine | murine(H-2 IA^b) | [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCRs for two clonotypes was Vβ3 and Vβ8.1-2
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(199–211)	Env(204–216)	SVITQACSKVSFE	Vaccine	Rhesus macaque( )	[Nehete1993]

Vaccine: *Vector/type:* peptide

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice
- A weak or transient proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys

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gp160(199–211)	Env(204–216)	SVITQACSKVSFE	HIV-1 infection	human, chimpanzee( )	[Nehete1998a]

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env

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gp160(199–211)	gp120(204–216)	SVITQACSKVSFE	Vaccine	murine(H-2^{bxk,sxd})	[Sastry1991]

Vaccine: *Vector/type:* peptide

- Peptides induced T-cell proliferative response in mice representing four haplotypes

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gp160(200–214)	gp120(205–219 LAI)	VITQACPKVSFEPIP	Peptide-HLA interaction	human(HLA-DR)	[Gaudebout1997]

- Peptide binds to both HLA-DR*1101 and HLA-DR*0401 with high affinity
- Because of the distinctive binding pockets of HLA-DR*1101 and HLA-DR*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding

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gp160(201–212)	Env( )	ITQACPKVSFEP	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was Vβ3
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (TSVITQACPKVSFEP and ITQACPKVSFEPIPI)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

gp160(201–215) Env( ) TSVITQACPKVSFEPIPI Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was Vβ6
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

gp160(206–220) Env( ) PKVSFEPIPIHYCAP Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of 1007 (US, clade B) and 12 hybridomas recognized the peptide with Vβ usage of Vβ4, 6, 7, 8.1-2, 8.3, 11, 12 and others not determined
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41

- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(206–230) gp120(206–230) PKVSFEPIPIHYCAPAG-FAILKCNN Vaccine murine(H-$2^{d,b}$) [Sjolander1996]

Vaccine: *Vector/type:* recombinant protein *HIV component:* gp160

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein

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gp160(208–220) Env( ) ITFEPIPIHYC Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of UG92005 (UG, clade D) and its was recognized by two hybridomas with Vβ usage Vβ12 and not determined
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (PKITFEPIPIHYCAP and ITFEPIPIHYCAPAG)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(208–222) Env( ) ITFEPIPIHYCAPAG Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of UG92005 (UG, clade D) and it was recognized by five hybridomas with Vβ usage Vβ5, 8.2, 12 and not determined
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(210–223) gp120(215–228) FEPIPIHYCAFPGF Vaccine murine(H-2^{bxk}) [Sastry1991]

Vaccine: *Vector/type:* peptide

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160

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gp160(212–231) gp120(221–240 W6.ID) PIPIHYCAPAGFAILKC-NNK Vaccine human( ) [Jones1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* W61D *HIV component:* gp120 *Stimulatory Agents:* QS21/MPL adjuvant

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated
- Two T-cell lines react specifically with this peptide

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gp160(214–220) Env( ) PIHYCAP Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was not determined
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (PKVSFEPIPIHYCAP and PIHYCAPAGFAILKC)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined

- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(215–225) Env( ) IHYCAPAGFAI Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was not determined
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (EPIPIHYCAPAGFAI and IHYCAPAGFAILKCN)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(216–225) Env( ) HYCAPAGFAI Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C2 region of UG92005 (UG, clade D) and Vβ usage of its TCR was not determined
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (EPIPIHYCAPAGFAI and HYCAPAGFAILKCND)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(220–234) gp120(225–240 SF2) PAGFAILKCNNKTFN *in vitro* stimulation ( ) [Manca1993]

- T-cell line derived from unprimed, uninfected individual
- Responds to APC pulsed with either synthetic peptide or gp120
- Human MAbs 448-D and 450-D enhance APC gp120 uptake and presentation

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gp160(220–235) gp120( ) PAGFAILKCNNKTFNY *in vitro* stimulation human(DR2) [Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein
- gp120 priming induced T-cells that recognize this peptide

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gp160(220–235) gp120(220–235 HXB2) PAGFAILKCNNKTFNY *in vitro* stimulation human(DR2) [Guzman1998]

- *Listeria monocytogenes*, an intracellular pathogen which is ingested by macrophages and can escape from the phagosome to replicate in the cytoplasm, was used successfully as carrier to deliver this gp120 epitope to CD4+ T-cells

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gp160(220–235) gp120(191–205 HXB2) PAGFAILKCNNKTFNY *in vitro* stimulation human(DR2) [Fenoglio1999]

- gp120 pep24 epitope exhibited antagonistic activity against proliferation of gp120-specific T-cells when flanked by unrelated amino acid sequence
- The glutathione S-transferase (GST)-peptide system can be used to display peptides; antigenicity was maintained when this peptide was expressed at the C-term end, but antagonism resulted when this peptide was expressed at the N-term end

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gp160(223–231)	gp120(238–246 HXB2)	FAILKCNNK	*in vitro* stimulation	human( )	[LiPira1998]

- Clonal heterogeneity was broad for a recall response to tetanus toxoid or PPD, but oligoclonal to primary HIV antigens, dominated in this case by TCR Vβ 22 usage
- Donor of PBMC that recognized this epitope had HLA-DR alleles 2 and 6
- The only (detected) immunogenic variant of this epitope was derived from strain NOF (YAILKCNNK)

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gp160(223–231)	gp120(194–202 HXB2)	FAILKCNNK	*in vitro* stimulation	human(DR2,6)	[Manca1996]

- Epitope was the minimal stimulatory sequence defined for two Th lines stimulated *in vitro*
- One Th line was stimulated by gp120, one by a Glutathione-S-transferase (GST)-peptide fusion
- Alanine substitutions at position 914, 196, and 202 abrogated activity for the GST-peptide stimulated line, but not for a gp120 stimulated line
- Constructs combining GST and the PAGFAILKCNNKTFNY gp120 peptide at the C-term end of GST stimulated Th cells but not at the N-term end

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gp160(223–231)	gp120(194–202 HXB2)	FAILKCNNK	*in vitro* stimulation	human(DR2,6)	[Manca1996]

- Epitope was the minimal stimulatory sequence defined for two Th lines stimulated *in vitro*
- One Th line was stimulated by p66, one by a Glutathione-S-transferase (GST)-peptide fusion protein
- Alanine substitutions at position 914, 196, and 202 abrogated activity for the GST-peptide stimulated line, but not for a gp120 stimulated line
- Constructs linking GST to the PAGFAILKCNNKTFNY gp120 peptide at the C-term end of GST stimulated Th cells, constructs linking at the N-term end did not
- The C and N termini of GST are not intrinsically permissive or non-permissive, presentation is epitope specific (see SSTVNDIQKLV for contrast)

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gp160(223–231)	gp120(237–245 SF2 HXB2)	FAILKCNNK		murine BALB/c(H-2^d)	[Fenoglio2000a]

- This peptide is an immunodominant Th epitope in BALB/c mice
- Substitutions in positions 237, 241, 243, 244 with Ala all cause reduced recognition
- Most natural analogs they tested did not cross-react, including peptides based on clade A, B, C, D, E and O sequences
- Position 237 and 244 when substituted with Ala cause an antagonistic response and the natural analogues of this epitope to loose antigenicity
- Some of the naturally occurring variants also cause an antagonistic response

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gp160(230–245)	gp120( )	NKTFNGKGPCTNVSTY	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(235–247)	gp120(240–252)	GTGPCTNVSTVQC	Vaccine	Rhesus macaque( )	[Nehete1993]

Vaccine: *Vector/type:* peptide

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice
- Proliferative response to this peptide was observed in 1/3 immunized rhesus monkeys, with a weak transient response in the other two

gp160(240–255)	gp120( )	TNVSTVQCTHGRPIY	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*

gp160(242–261)	gp120(242–261 IIIB)	VSTVQCTHGIRPVVST-QLLL	SHIV infection	Rhesus macaque(DRB1*0406)	[Lekutis1997b]

- A novel C2 region Th epitope was described in SHIV-89.6 infected Macaca mulatta

gp160(250–265)	gp120( )	GIRPIVSTQLLLNGSC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

gp160(264–287)	gp120(269–292 NL43)	SLAEEEVVIRSANFTD-NAKTIIVQ	Vaccine	human( )	[Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients
- 50% of vaccinees had a stimulation index of greater than 5 to this peptide

gp160(269–283)	gp120(269–283 IIIB B10)	EVVIRSANFTDNAKT	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(270–285)	gp120( )	VVIRSDNFTNNAKTIC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

gp160(274–288)	gp120(274–288 IIIB B10)	SANFTDNAKTIIVQL	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(280–296)	gp120( )	NAKTIIVQLNESVAIC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

gp160(289–297)	gp120(292–300 SF2)	NESVAINCT	Vaccine	human( )	[Botarelli1991]

Vaccine: *Vector/type:* recombinant protein *Strain:* SF2 *HIV component:* gp120

- A non-glycosylated form of SF2 gp120, env 2-3, was used as an immunogen – 20% of T-cell clones do not recognize the glycosylated form

gp160(290–306)	gp120(296–312 LAI)	SVVEINCTRPNNNTRK-S	HIV-1 infection	human( )	[Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

gp160(296–314)	gp120(303–321 IIIB)	CTRPNNNTRKSIRIQR-GPG(Y)	Vaccine	goat( )	[Palker1989]

Vaccine: *Vector/type:* peptide *Strain:* IIIB

- Goats were immunized with peptides containing V3 type-specific neutralizing determinants coupled to T1

gp160(297–321)	gp120(302–324 MN)	TRPNYNKRKRIHIGPG-RAFYTTK	Vaccine	murine BALB/c(H-2^d)	[Oscherwitz1999a]

Vaccine: *Vector/type:* peptide *Strain:* MN *HIV component:* V3

- Epitope presented as a tandem repeat (eight copies) elicits stronger B-cell and T-cell responses than the epitope presented as a single copy
- This study indicates that the increased response was not due to neodeterminants created at the junction of the peptides, but rather due to an epitope density effect, increased immunogenicity through a high ratio of epitope to protein

gp160(297–330)	Env(303–335 BX08)	TRPNNNTRKSIHIGPG-RAFYATGEIIGDIRQAH	Vaccine	human( )	[Gahery-Segard2000a]

Vaccine: *Vector/type:* lipopeptide

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 6/10 reacted to this peptide
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in five vaccinees
- None of the 12 tested had an IgG response to gp120 or gp160 and vaccinees could be differentiated from HIV-1 seropositive individuals with a commercial HIV detection kit – no neutralizing antibodies were observed

gp160(298–307)	Env( )	RPYNNTRKGI	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by a hybridoma with Vβ usage not determined
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (TINCTRPYNNTRKGI and RPYNNTRKGIHIGPG)

- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(301–325) gp120( ) NNTRKSIRIQRGPGRA-FVTIGKIGN Vaccine murine( ) [Sasaki1998a]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* Env, Rev *Stimulatory Agents:* QS-21 adjuvant

- The env response is what is being sought, but co-expression of rev is required
- Intramuscular versus nasal vaccination with DNA vaccine with a QS-21 adjuvant was studied
- QS-21 enhanced the IgG2a response mediated via Th1 cytokines IFNγ and IL-2 and delayed type hypersensitivity (DTH) in response to the V3 peptide was measured by a foot pad swelling test [Sasaki1998a]

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gp160(302–315) gp120(307–322 IIIB) NTRKSIRIQRGPGR Vaccine murine( ) [Goodman-Snitkoff1990]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3

- Identification of putative Th epitopes that can stimulate an antibody response in peptide-immunized mice

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gp160(305–321) gp120(312–329) (CG)KSIRIQRGPGRAF-VTIG HIV-1 infection human( ) [Adams1997]

- Used as positive control in study examining T-cell response to four p24 Gag peptides

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gp160(308–319) gp120( ) (CKR)KIHIGPGQAFYT HIV-1 infection murine(H-$2^{b,d,k,s}$) [Ahluwalia1997b]

- A V3 loop peptide modified to resemble an Indian form (GPGQ) was incorporated into ISCOMS (immune stimulating complexes) or liposomes, and used to immunize mice – the IgG2a/IgG2b Ab response was enhanced by the presentation in the ISCOM suggestive of a Th1 response

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gp160(308–321) gp120( ) RIHIGPGRAFYTTK Vaccine murine(H-2^d) [Klinman1995]

Vaccine: *Vector/type:* peptide *Strain:* MN *HIV component:* V3

- Epitope name: SP10. Hybrid T1-V3 peptide activates IL-4 and IL-6 in a dose dependent manner
- 10-mer from V3 contributes to this response

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gp160(308–322) gp120(308–322 IIIB) RIHIGPGRAFYTTKN human( ) [Furci1997]

- 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but only 1/11 exposed-uninfected individuals recognized this peptide
- 1/18 unexposed-uninfected controls could recognize this peptide
- Erroneously documented as IIIB sequence - most likely MN peptide

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK Vaccine Rhesus macaque( ) [Nehete1993]

Vaccine: *Vector/type:* peptide

- Epitope name: P18. Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice
- Despite the proliferative response to this peptide in mice and humans, no response was observed in 3 rhesus monkeys

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 infection human( ) [Wasik1997a]

- Epitope name: P18. The breadth and intensity of the CTL response and the type of Th response was studied in seven rapidly progressing HIV-1+ infants
- IL-2 and γ IFN production from Th1 cells correlated with the CTLp frequency against HIV-1 Gag, Env, Nef and Pol
- IL-4 production from Th2 cells was inversely correlated with the CTLp frequency
- The HIV-1+ children with strong CTL responses had levels of anti-CD3 MAb induction of Th1 cells comparable to uninfected children
- The children that did not mount a good CTL response had dramatically decreased numbers of Th1 relative to Th2 cells

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 infection human( ) [Wasik2000a]

- Epitope name: P18. Th responses measured by IL-2 responses to P18 and T1 in HIV-1 infected infants were undetectable at less than 1 month of age, and remained low in children with AIDS symptoms, but increased with age in children with slowly progressive disease
- The kinetics and intensity of the CTL activity during the first year of life was related to the child's ability to make Th1 responses

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 exposed seronegative human( ) [Pinto1995a]

- Epitope name: P18. CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers

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gp160(308–322) gp120(315–329 MN) RIHIGPGRAFYTTKN HIV-1 exposed seronegative human( ) [Pinto1995a]

- Epitope name: P18. CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 infection human( ) [Clerici1989]

- Epitope name: P18. IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 infection human( ) [Clerici1991a]

- Epitope name: P18. Peptides stimulate Th cell function and CTL activity in similar patient populations

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	human( )	[Clerici1991b]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK		human( )	[Clerici1992]

- Epitope name: P18. Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	HIV-1 infection	human( )	[Clerici1997]

- Epitope name: P18. used in a study of the influence of pentoxifylline on HIV specific T-cells

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gp160(308–322)	gp120( )	RIHIGPGRAFYTTKN		human( )	[Clerici1992]

- Epitope P18 MN: Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men

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gp160(308–322)	gp160(315–329 IIIB)	RIQRGPGRAFVTIGK	HIV-1 exposed seronegative, HIV-1 infection	human( )	[Wasik1999a]

- Epitope name: P18. IL-2 responses associated with β-chemokine expression were detectable at birth in the majority of uninfected infants born to HIV+ mothers, declining by age 6 months
- In both uninfected and infected infants of HIV-positive mothers, responses to the T1 peptide (KQIINMWQEVGKAMYA) were more frequent than responses to P18
- T1 is a highly conserved epitope, whereas P18 has a higher mutation rate due to its location in the immunodominant V3 loop region

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	HIV-1 exposed seronegative	human( )	[Kaul1999a]

- Epitope name: P18. Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- The helper epitopes used in this study were noted to be previously described [Clerici1989], and were not explicitly described in [Kaul1999a]

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	HIV-1 exposed seronegative, HIV-1 infection	human( )	[Kuhn2001]

- Epitope name: P18. In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL-2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4
- The mothers were predominantly infected subtype C but the T-helper response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents
- 3/33 infants with cord blood T-helper responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected – 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding
- Measurable HIV specific T-helper responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1

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gp160(308–322)	gp120(315–329 MN)	RIHIGPGRAFYTTKN	HIV-1 exposed seronegative, HIV-1 infection	human( )	[Kuhn2001]

- Epitope name: P18. In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL-2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4
- The mothers were predominantly infected subtype C but the T-helper response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents
- 3/33 infants with cord blood T-helper responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected – 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding
- Measurable HIV specific T-helper responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	HIV-1 infection	human(DR)	[Baier1995]

- Epitope name: P18. Linked HIV-1 T1 and P18 peptides to anti-HLA-DR and IgD Fab fragments to enhance uptake by antigen presenting cells thus increase immunogenicity

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2 A^d)	[Takahashi1990]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. Induces both class II restricted CD4+ Th cells, and class I restricted CD8+ CTL

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Peptide-HLA interaction	murine(H-2 I-A^d)	[Takeshita1995a]

- Epitope name: P18. Binds Class II H-2 I-A^d requiring riqrgPgRaFvti, and Class I H-2 D^d, requiring iGPgRaFvtI

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gp160(308–322)	Env( )	RIQRGPRAFVTIGK	Vaccine	murine(H-2^d)	[Lu1999a]

Vaccine: *Vector/type:* DNA, CMV promotor *Strain:* IIIB *HIV component:* gp160, Rev *Stimulatory Agents:* MIP-1α expression vector

- Epitope name: P18. MIP-1α expression plasmid co-inoculated with a DNA vaccine consisting of HIV-1 pCMV160IIIB and pcRev enhanced the HIV-specific T-cell immune response as measured by a CTL test against using V3 peptide pulsed targets, and a DTH test to V3 peptide.
- The IgG1/IgG2a response was lowered with co-inoculation of MIP-1α, suggesting it preferentially elicits a Th1 response

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gp160(308–327)	gp120(306–325 MN)	RIHIGPGRAFYTTKNII-GIT	HIV-1 infection	human(DRB1*0101)	[Hayball1997]

- Tandem repeated presentation of epitope enhances binding to class II molecule and therefore induction of T-cell proliferation
- Tandem peptides are thought to enhance proliferation through improved recruiting of CD4 to the activation complex, which can counter-balance gp120's sequestering of CD4 and consequential inhibition of a proliferative response

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gp160(309–323)	gp120(309–323 IIIB B10)	EQRGPGRAFVTIGKI	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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gp160(309–325) gp120(314–330) IQRGPGRAFVTIGKIGN HIV-1 infection human( ) [Caruso1997]

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24

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gp160(311–320) gp120( ) RGPGPAFVTI Vaccine murine(H-2^d) [Xin1998]

Vaccine: *Vector/type:* DNA, CMV promotor *Strain:* IIIB *HIV component:* gp160, Rev *Stimulatory Agents:* IL-2 expression vector

- Intranasal immunization with IL-2 expression plasmid in addition to DNA vaccine amplifies cellular response to antigen, probably via activation of Th type 1 (Th1) cells

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gp160(311–320) gp120( ) RGPGPAFVTI Vaccine murine(H-2^d) [Xin1999a]

Vaccine: *Vector/type:* DNA, CMV promotor *Strain:* IIIB *HIV component:* gp160, Rev *Stimulatory Agents:* IL-15 expression vector

- Intranasal immunization with IL-15 expression plasmid in addition to DNA vaccine increases DTH response and CTL activity to the antigen, and decreases the serum IgG1 to IgG2a ratio, enhancing Th type 1 (Th1) cell-mediated immunity
- Expression of IL-2 or IL-15 can enhance Th1 response to the vaccine, but they to do not appear to elicit a synergistic response

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gp160(311–320) gp120( ) RGPGPAFVTI Vaccine murine(H-2^d) [Ihata1999a]

Vaccine: *Vector/type:* DNA, CMV promotor *Strain:* IIIB *HIV component:* gp160, Rev *Stimulatory Agents:* CD40L expression vector

- CD40L expression increases DTH, and Th1-dependent responses based on enhanced IgG2a titers, with no lowering of IgG1 titers
- Elispot assay indicated co-injection with hCD40L resulted in greater numbers of IFN-γ producing Th1cells, as well as increased IL-4 producing Th2 cells
- Results suggest hCD40L enhances both Th1 and Th2 cells, and such a pattern of induction is unique among adjuvants, as most adjuvants increase either Th1 or Th2

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gp160(311–322) Env( ) RGPGRAFVTIGK Vaccine murine(H-2^d) [Kusakabe2000]

Vaccine: *Vector/type:* DNA, CMV promotor *Strain:* IIIB *HIV component:* gp160, Rev *Stimulatory Agents:* pGM-CSF expression vector

- The timing of delivery of the pGM-CSF expression plasmid for intramuscular DNA pCMV160IIIB/Rev vaccination impacts the Th response, maximizing Th2 responses when administered 3 days prior to the DNA vaccine, and Th1 responses when administered 3 days after the DNA vaccine

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gp160(314–328)	gp120(314–328 IIIB B10)	GRAFVTIGKIGNMRQ	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(314–341)	gp120(319–346 NL43)	GRAFVTIGKIGNMRQ-AHCNISRAKWNAT	Vaccine	human( )	[Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients
- More than 25% of vaccinees had a stimulation index of greater than 5 to this peptide

gp160(315–328)	Env( )	RAYYTTNIVGNIRQ	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by two hybridomas with Vβ usage not determined, but one used Vα 8
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

gp160(317–331)	gp160(324–338 IIIB)	FVTIGKIGNMRQAHC	Vaccine	murine(H-2^k, H-2^d)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- B10.BR (H-$2A^k$, E^k) and B10.D2 (H-$2A^d$, E^d) mice immunized with rec gp160 showed a proliferative response to this peptide
- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes including FVTIGKIGNMRQAHC and is referred to as a "multideterminant region" or cluster peptide

gp160(317–331)	gp120(324–338 IIIB)	FVTIGKIGNMRQAHC	Vaccine	murine(H-$2^{k,d}$)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(317–349)	gp160(324–356 IIIB)	FVTIGKIGNMRQAHC-NISRAKWNNTLKQIDS-KL	HIV-1 infection, Vaccine	human, murine(H-2^k, H-2^d)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people
- This cluster peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k) and B10.D2 mice (H-2A^d, E^d), but shorter peptides from within this region stimulated H-2^k, H-2^d, H-2^b and H-2^s responses
- IL-2 production in response to this peptide was observed in 58% (21/36) of asymptomatic HIV-infected individuals

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gp160(319–338)	gp120(320–339 89.6)	RRNIIGDIRQAHCNISR-AKW	Vaccine	murine(H-2^k, H-2^d)	[Dai2001]

Vaccine: *Vector/type:* recombinant protein *Strain:* 89.6 *HIV component:* gp120 *Stimulatory Agents:* mutant R192G heat-labile toxin from *E. coli* as adjuvant

- Promiscuous immunodominant epitope in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence
- This peptide was recognized by 7/10 CBA/J and 7/10 BALB/c mice with SI $>$ 4, averaging 6.3 and 4.8, and is considered to be promiscuously immunodominant
- Uniquely immunodominant sequences tended to be in the interior of the protein

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gp160(321–336)	gp120( )	RIIGDIRKAHCNISRY	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(322–336)	Env( )	IIGDIRQAHCNISRE	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V3 region of 1007 (US, clade B) and was recognized by three hybridomas with Vβ usage Vβ 6 and not determined
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(322–336) Env( ) IVGNIRQAHCNVSKA Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by three hybridomas with Vβ usage Vβ 6, 8.1, and not determined
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(324–336) Env( ) GNIRQAHCNVSKA Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by two hybridoma with Vβ usage Vβ8.2 and not determined

- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (IVGNIRQAHCNVSKA and GNIRQAHCNVSKAKW)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(324–338) Env( ) GNIRQAHCNVSKAKW Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by eleven hybridomas with Vβ usage Vβ5, 7, 8.1, 8.2, 11 and not determined – a Vβ 8.1's and Vβ 8.2 also were shown to use Vα 8, and one of the ND used Vα 2
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(327–341)	gp120(327–341 HXB2)	RQAHCNISRAKWNNT	Vaccine	murine(I-A^d)	[Warren1992]

Vaccine: *Vector/type:* recombinant protein *Strain:* HXB2 *HIV component:* gp120

- Minimum epitope and MHC restriction determined for CTL clone that recognizes the N-terminal flank of the V3 loop

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gp160(331–345)	gp120( )	CNISRAQWNNTLEQI	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(332–354)	gp120(337–359 NL43)	NISRAKWNATLKQIAS-KLREQFG	Vaccine, HIV-1 infection	human( )	[Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients
- More than 30% of vaccinees had a stimulation index of greater than 5 to this peptide

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gp160(335–349)	gp160(342–356 IIIB)	RAKWNNTLKQIDSKL	Vaccine	murine(H-2^k, H-2^b, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- B10.BR (H-2A^k, E^k), B10.A(5R) (H-2A^b, E^b) and B10.S(9R) (H-2A^s, E^s) mice immunized with rec gp160 showed a proliferative response to this peptide
- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes including RAKWNNTLKQIDSKL and is referred to as a "multideterminant region" or cluster peptide

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gp160(335–349)	gp120(342–356 IIIB)	RAKWNNTLKQICSKL	Vaccine	murine(H-2^{k,t4,i5})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(339–359)	gp120(340–359 89.6)	NNTLQQIVIKLREKFR-NKTI	Vaccine	murine(H-2^k, H-2^d)	[Dai2001]

Vaccine: *Vector/type:* recombinant protein *Strain:* 89.6 *HIV component:* gp120 *Stimulatory Agents:* mutant R192G heat-labile toxin from *E. coli* as adjuvant

- Promiscuous immunodominant epitope in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence
- This peptide was recognized by 4/10 CBA/J and 6/10 BALB/c mice with SI $>$ 4, averaging 4.9 and 5.5 and is considered to be promiscuously immunodominant
- Uniquely immunodominant sequences tended to be in the interior of the protein

gp160(341–356)	gp120( )	TLEQIVKKLREQFGNC	*in vitro* stimulation	human( )	[Manca1995b]
• Peptide stimulation of PBMC from non-infected individuals *in vitro* • Peptide priming does not always induce T-cells that recognize whole protein					
gp160(344–357)	gp120(346–359)	QIVKKLREQFGNNK	HIV-1 infection	human( )	[Krowka1990]
• Conjugation of HIV peptides to liposomes and rIL-2 stimulation may enhance cell-mediated responses					
gp160(353–360)	gp120(355–362 IIIB)	FGNNKTII	SHIV infection	Rhesus macaque( )	[Lekutis1997b]
• C3 region minimal epitope determined through fine epitope mapping • Cell line was lost prior to confirmation of MHC requirements					
gp160(363–372)	gp120(368–377 LAI)	QSSGGDPEIV	HIV-1 infection	human( )	[Schrier1989]
• Stimulates T-cell proliferation in HIV-infected donors					
gp160(364–378)	gp120(364–378 IIIB B10)	SSGGKPEIVTHSFNC	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses					
gp160(369–383)	gp120(369–383 IIIB B10)	PEIVTHSFNCGGEFF	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses					
gp160(381–395)	gp120( )	EFFYCNTTQLFNNTW	*in vitro* stimulation	human( )	[Manca1995b]
• Peptide stimulation of PBMC from non-infected individuals *in vitro* • Peptide priming does not always induce T-cells that recognize whole protein					
gp160(394–408)	gp120(394–408 IIIB B10)	TWFNSTWSTKGSNNT	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]
• 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses					
gp160(396–411)	gp120( )	FNNTWRLNHTEGTKG-C	*in vitro* stimulation	human( )	[Manca1995b]
• Peptide stimulation of PBMC from non-infected individuals *in vitro* • Peptide priming does not always induce T-cells that recognize whole protein					

gp160(399–413)	gp120(399–413 IIIB B10)	TWSTKGSNNTEGSDT	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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gp160(404–423)	gp120(400–419 89.6)	GTNGTEGNDIITLQCRIKQI	Vaccine	murine(H-2^k, H-2^d)	[Dai2001]

Vaccine: *Vector/type:* recombinant protein *Strain:* 89.6 *HIV component:* gp120 *Stimulatory Agents:* mutant R192G heat-labile toxin from *E. coli* as adjuvant

- Promiscuous immunodominant epitope in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence
- This peptide was recognized by 4/10 CBA/J and 6/10 BALB/c mice with SI $>$ 4, averaging 4.9 and 5.5 and is considered to be promiscuously immunodominant
- Uniquely immunodominant sequences tended to be in the interior of the protein

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gp160(410–429)	gp120(410–429 PV22)	GSDTITLPCRIKQFINMWQE	HIV-1 infection	human(DR4)	[Callahan1990]

- Synthetic peptides representing natural variants were used to test for recognition in the context DR4

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gp160(410–429)	gp120(410–429 PV22)	GSDTITLPCRIKQFINMWQE	HIV-1 infection	human(DR4(Dw10))	[Polydefkis1990]

- Human CD4+ T-cell clones lyse recombinant vaccinia virus-infected cells that synthesize envelope gp160

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gp160(416–431)	gp120( )	LPCRIKQIINMWQEVY	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(418–436)	Env(417–435)	CRIKQIINMWQGVGKAMYA	HIV-1 infection	human, chimpanzee( )	[Nehete1998a]

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env

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gp160(421–436)	gp120(426–441 IIIB)	KQFINMWQEWGKAMYA		human( )	[Furci1997]

- Epitope T1 variant: 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but none reacted with this previously defined epitope
- IIIB position 435 listed as "W" in this epitope as opposed to "V" in the sequence

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gp160(421–436)	gp120(428–433 IIIB)	KQIINMWQEVGKAMYA	HIV-1 infection	human( )	[Wasik2000a]

- Epitope name: T1. Th responses measured by IL-2 responses to P18 and T1 in HIV-1 infected infants were undetectable at less than 1 month of age, and remained low in children with AIDS symptoms, but increased with age in children with slowly progressive disease
- The kinetics and intensity of the CTL activity during the first year of life was related to the child's ability to make Th1 responses

gp160(421–436) gp120(428–433 IIIB) KQIINMWQEVGKAMYA HIV-1 infection human( ) [Wasik1997a]
- Epitope name: T1. The breadth and intensity of the CTL response and the type of Th response was studied in seven rapidly progressing HIV-1+ infants
- IL-2 and γ IFN production from Th1 cells correlated with the CTLp frequency against HIV-1 Gag, Env, Nef and Pol
- IL-4 production from Th2 cells was inversely correlated with the CTLp frequency
- The HIV-1+ children with strong CTL responses had levels of anti-CD3 MAb induction of Th1 cells comparable to those of uninfected children

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA Vaccine human( ) [Berzofsky1988]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160
- Epitope name: T1. Proliferative response to T1 and T2 peptides in 14 immunized, uninfected humans

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA Vaccine goat( ) [Palker1989]

Vaccine: *Vector/type:* peptide *Strain:* IIIB
- Epitope name: T1. Goats immunized with peptides containing V3 type-specific neutralizing determinants coupled to T1

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA HIV-1 infection human( ) [Clerici1989]
- Epitope name: T1. IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA HIV-1 infection human( ) [Clerici1991a]
- Epitope name: T1. Peptides stimulate Th cell function and CTL activity in similar patient populations

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA Vaccine human( ) [Clerici1991b]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160
- Epitope name: T1. Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA HIV-1 exposed seronegative human( ) [Clerici1992]
- Epitope name: T1. Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA Vaccine murine( ) [Veronese1994]

Vaccine: *Vector/type:* bacteriophage coat protein *Strain:* MN *HIV component:* V3
- Epitope T1 was engineered into a filamentous bacteriophage coat protein, and the Th epitope stimulated Ab production to the V3 loop

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gp160(421–436) gp120(428–443 IIIB) KQIINMWQEVGKAMYA Vaccine chimpanzee( ) [Haynes1993]

Vaccine: *Vector/type:* peptide *Strain:* IIIB
- Epitope name: T1. Hybrid T1-V3 peptide immunogenicity reduced when the fusogenic domain of gp41 was added

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gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	HIV-1 infection	human( )	[Clerici1997]

- Epitope name: T1. Used in a study of the influence of pentoxifylline on HIV specific T-cells

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	HIV-1 exposed seronegative	human( )	[Pinto1995a]

- Epitope name: T1. CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers

gp160(421–436)	gp160(428–433 IIIB)	KQIINMWQEVGKAMYA	HIV-1 exposed seronegative, HIV-1 infection	human( )	[Wasik1999a]

- Epitope name: T1. IL-2 responses associated with β-chemokine expression were detectable at birth in the majority of uninfected infants born to HIV+ mothers, declining by age 6 months
- T1 peptide: In both uninfected and infected infants of HIV-positive mothers, responses to the T1 peptide were more frequent than responses to P18 (RIQRGPGRAFVTIGK)
- T1 is a highly conserved epitope, whereas P18 has a higher mutation rate due to its location in the immunodominant V3 loop region

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	HIV-1 infection	human( )	[Kaul1999a]

- Epitope name: T1. Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described [Clerici1989], and were not explicitly described in [Kaul1999a]

gp160(421–436)	gp120( )	KQIINMWQEVGKAMYA	HIV-1 infection, Vaccine	human( )	[Bartlett1998a]

Vaccine: *Vector/type:* peptide *Strain:* MN *HIV component:* polyepitope

- Epitope name: T1. C4-V3 PV (polyvalent HIV envelope synthetic peptide immunogen) consisted of T1 helper epitope presented in tandem with a V3 loop CTL epitope from one of four different North American strains
- This was a pilot phase I study involving vaccination of ten HIV-infected subjects who were HLA-B7-positive
- Enhanced lymphoproliferative response to peptide was observed in 5/8 vaccinees – increase in neutralizing antibody responses in 4/8 vacinees

gp160(421–436)	gp120( )	KQIINMWQEVGKAMYA	HIV-1 exposed seronegative, HIV-1 infection	human( )	[Kuhn2001]

- Epitope name: T1. In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL-2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4
- The mothers were predominantly infected subtype C but the T-helper response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents
- 3/33 infants with cord blood T-helper responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected – 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding
- Measurable HIV specific T-helper responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	Vaccine peptide IIIB	human(DR)	[Baier1995]

- Epitope name: T1. Linked HIV-1 T1 and P18 peptides to anti-HLA-DR and anti-IgD Fab fragments to enhance uptake by antigen presenting cells and thus increase immunogenicity

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	Vaccine	murine(H-2$E\alpha E\beta^k$)	[Boehncke1993]

Vaccine: *Vector/type:* peptide *Strain:* IIIB

- Epitope name: T1. C3H H2^k mice were used for immunization in the study because H-2^k mice are particularly good T1 responders – T1 can be presented by $E\alpha E\beta^k$ but not $E\alpha E\beta^b$ – the nature of the T1 class II molecular interaction was thoroughly explored
- Alanine substitutions across peptide did not negatively affect MHC binding or effective presentation of epitope, except at three critical residues (432N, 435Q, 439K), however substitutions with larger side chains often diminished activity – only a few amino acids were found to be critical for class II interaction and for maintaining T-cell receptor specificity
- A gain in potency was observed when 436E was replaced with A, suggesting that substitutions in positions that interfere with binding might allow the design of a more potent vaccine

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	Vaccine	murine(H-2^d)	[Klinman1995]

Vaccine: *Vector/type:* peptide *Strain:* IIIB

- Epitope name: T1. Hybrid T1-V3 peptide activates IL-4 and IL-6 in a dose dependent manner

gp160(421–436)	gp160(428–443 IIIB)	KQIINMWQEVGKAMYA	Vaccine	murine(H-2^k, H-2^s, H-2^d)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- B10.BR (H-2A^k, E^k), B10.D2 (H-2A^d, E^d) and B10.S(9R) (H-2A^s, E^s) mice immunized with rec gp160 showed a proliferative response to this peptide
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including KQIINMWQEVGKAMYA and is referred to as a "multideterminant region" or cluster peptide

gp160(421–436)	gp120(428–443 IIIB B10)	KQIINMWQEVGKAMYA	computer prediction	murine(H-2^{k,d,s})	[Cease1987a]

- Epitope name: T1. 1 of 2 functional epitopes identified using an amphipathic helix epitope prediction algorithm

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	Vaccine	murine(H-2^{k,d,t4})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Epitope name: T1. Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMYA	Vaccine	murine(H-2^k)	[Ahlers1997b]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* polyepitope

- Epitope name: T1. First identified Th epitope in HIV

- Alanine at position 436 (instead of E in wild-type) enhances MHC binding and antigenicity of peptide by several orders of magnitude
- Vaccines with a CTL epitope linked to a more potent helper epitope yielded greatly enhanced CTL response relative to the wildtype helper epitope
- T1 peptide linked to CTL epitopes in four vaccine constructs used to immunize mice: KQIINMWQEVGKAMYAPPIS-GQIRRIQRGPGRAFVTIGK, KQIINMWQEVGKAMYAPPISGQIRRIQRGPGRAFVTI, KQIINMWQAVGKAMYAPPISGQIR-RIQRGPGRAFVTIGK, KQIINMWQAVGKAMYAPPISGQIRRIQRGPGRAFVTI

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gp160(421–444) | gp160(428–451 IIIB) | KQIINMWQEVGKAMYAP-PISGQIR | HIV-1 infection, Vaccine | human, murine(H-2^k, H-2^b, H-2^s, H-2^d) | [Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people
- This cluster peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)
- IL-2 production in response to this peptide was observed in 73% (8/11) of asymptomatic HIV-infected individuals

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gp160(421–444) | gp120(428–451 IIIB) | KQIIMNWQEVGKAMYAP-PISGQIR | Vaccine | murine(H2^d) | [Shirai1996a]

Vaccine: *Vector/type:* peptide *Strain:* IIIB

- Epitope name: T1. Linked to a CTL epitope from hepatitis C virus, induced CD4+ helper cells producing IL-2

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gp160(423–440) | gp120(428–445) | FINMWQEVGKAMYAPPIS | HIV-1 infection | human( ) | [Caruso1997]

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24

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gp160(424–438) | gp120(424–438 IIIB B10) | INMWQEVGKAMYAPP | HIV-1 infection | human( ) | [Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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gp160(425–439) | gp120(432–446 IIIB) | NMWQEVGKAMYAPPI | Vaccine | murine(H-2^{t4}) | [Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(426–440)	gp160(432–446 IIIB)	NMWQEVGKAMYAPPI	Vaccine	murine(H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- B10.S(9R) (H-$2A^s$, E^s) mice immunized with rec gp160 showed a proliferative response to this peptide
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including NMWQEVGKAMYAPPI and is referred to as a "multideterminant region" or cluster peptide

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gp160(426–441)	gp120( )	MWQEVGKAMYAPPIG-C	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(430–444)	gp160(437–451 IIIB)	VGKAMYAPPISGQIR	Vaccine	murine(H-2^k, H-2^b, H-2^s, H-2^d)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-$2A^k$, E^k), B10.D2 mice (H-$2A^d$, E^d), B10.A(5R) mice (H-$2A^b$, E^b), and B10.S(9R) mice (H-$2A^s$, E^s)
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including VGKAMYAPPISGQIR and is referred to as a "multideterminant region" or cluster peptide

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gp160(430–444)	gp120(437–451 IIIB)	VGKAMYAPPISGQIR	Vaccine	murine(H-$2^{k,d,i5,t4}$)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(430–453)	gp120(430–453)	VGKAMYAPPISGQIRC-SSNITGLL	Vaccine	murine(H-2^b)	[Sjolander1996]

Vaccine: *Vector/type:* recombinant protein *HIV component:* gp160

- Study demonstrates that T-cell determinants from glycoproteins can depend on the glycosylation of the protein
- Peptide stimulation of an *in vitro* proliferative response required *in vivo* priming with glycosylated protein
- Local glycosylation sites thought not to be part of the epitope, but may be important for epitope processing

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gp160(433–447)	Env( )	AMYAPPIAGLIQCSS	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the C4 region of UG92005 (UG, clade D) and was recognized by ten hybridomas with Vβ usage Vβ 6, 8.1, 8.2, 13, 14 and not determined – among the ND Vβ set, three Vαs were identified, Vα 2, 8, and 11
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(433–447) Env( ) SNNTVGNPIILPCRI Vaccine murine(H-2 IA^b) [Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This epitope is located in the V4C4 region of 1007 (US, clade B) and was recognized by 13 hybridomas with Vβ usage Vβ 4, 7, 8.1, 8.2, 10, 12 and not determined – one of the Vβ 8.2 was shown to utilize Vα 2
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

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gp160(436–451) gp120( ) APPIGGQISCSSNITY *in vitro* stimulation human( ) [Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(438–460)	gp120(443–465 NL43)	PISGQIRCSSNITGLLL-TRDGGN	Vaccine	human( )	[Sitz1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* NL43 *HIV component:* gp120, gp160

- There was a great breadth of proliferative response to Env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients
- Close to 40% of vaccinees had a stimulation index of greater than 5 to this peptide

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gp160(439–448)	gp120(151–160 W6.ID)	IGGQIRCSSN	Vaccine	human( )	[Jones1999]

Vaccine: *Vector/type:* recombinant protein *Strain:* W61D *HIV component:* gp120 *Stimulatory Agents:* QS21/MPL adjuvant

- HIV-1 specific T-cell lines isolated from an HIV seronegative volunteer vaccinated with rgp120 and a QS21/MPL adjuvant
- One T-cell line responds to two overlapping peptides, and the region of overlap is IGGQIRCSSN
- The IIIB version of the first reactive peptide, EVGKAMYAPPIGGQIRCSSN, has a single substitution and induces proliferation as well as the original W61D peptide : `----------S--------`

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gp160(446–461)	gp120( )	SSNITGLLLTRDGGTC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(456–470)	gp120( )	RDGGTNVTNDTEVFRC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(459–473)	gp120(459–473 IIIB B10)	GNSNNESEIFRPGGG	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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gp160(468–483)	gp120(466–481)	FRPGGGDMRDNWRSE-L	HIV-1 infection	human( )	[Krowka1990]

- Conjugation of HIV peptides to liposomes and rIL-2 stimulation may enhance cell-mediated responses

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gp160(474–488)	gp120(474–488 IIIB B10)	DMRDNWRSELYKYKV	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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gp160(476–490)	gp160(483–497 IIIB)	RDNWRSELYKYKVVK	Vaccine	murine(H-2^k, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in B10.BR mice (H-2A^k and B10.S(9R) mice (H-2A^s, E^s)
- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes including RDNWRSELYKYKVVK and is referred to as a "multideterminant region" or cluster peptide

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gp160(476–490) | gp120(483–497 IIIB) | RDNWRSELYKYKVVK | Vaccine | murine(H-2^{d,t4}) | [Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(476–498) | gp160(483–506 IIIB) | RDNWRSELYKYKVVK-IEPLGVAPT | HIV-1 infection, Vaccine | human, murine(H-2^k, H-2^b, H-2^s, H-2^d) | [Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people
- This cluster peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)
- IL-2 production in response to this peptide was observed in 52% (14/27) of asymptomatic HIV-infected individuals

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gp160(482–501) | gp120(482–501 IIIB) | ELYKYKVVKIEPLGVA-PTKA | Vaccine | Rhesus macaque( ) | [Lekutis1997a]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* Env

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkey
- Epitope was recognized by both monkeys used in this study

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gp160(484–496) | gp120(484–496 HXB2) | YKYKVVKIEPLGV | Vaccine | Rhesus macaque(DR*W201) | [Lekutis1998]

Vaccine: *Vector/type:* DNA *Strain:* HXB2 *HIV component:* Env

- Variants of this epitope with substitutions at position 490(K) retained ability to bind to MHC class II, but failed to induce proliferation/cytokine secretion in HIV-1 env-specific CD4+ Th cells
- The modified peptide antagonized the wildtype peptide-induced proliferative response

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gp160(484–498) | gp120(484–498 IIIB B10) | YKYKVVKIEPLGVAP | HIV-1 infection | human( ) | [Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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gp160(484–499) | gp120(492–506 IIIB) | CKYKVVKIEPLGVAPT | Vaccine | murine(H-2^{d,k,t4,i5}) | [Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

gp160(485–498)	gp160(492–506 IIIB)	KYKVVKIEPLGVAPT	Vaccine	murine(H-2^k, H-2^b, H-2^s, H-2^d)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)
- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes including KYKVVKIEPLGVAPT and is referred to as a "multideterminant region" or cluster peptide

gp160(485–500)	gp120( )	KYKVIKIEPLGIAPTC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

gp160(486–494)	gp120(486–494 IIIB)	YKVVKIEPL	SHIV infection	Rhesus macaque(DRB*W201)	[Lekutis1997b]

- C5 region minimal epitope determined through fine epitope mapping

gp160(487–512)	gp120(494–518 IIIB)	KVVKIEPLGVAPTKAK-RRVVQREKRC	Vaccine	murine( )	[Goodman-Snitkoff1990]

Vaccine: *Vector/type:* peptide *Strain:* IIIB

- Identification of putative Th epitopes that stimulate an antibody response in peptide immunized mice

gp160(499–511)	gp120( )	TKAKRRVVEREKR	*in vitro* stimulation	human(DR)	[Wilson1997a]

- Thought to be a mimic of a HLA class II DR β chain variable region
- Response to this epitope may cause a breakdown of self-tolerance
- Presentation of epitope induced autoreactive T-cell lines in PBMC from uninfected donors
- Suppression of proliferation to soluble antigens by the CD8+ fraction of TKAKRRVVEREKR stimulated T-cells was observed

gp160(519–543)	Env(519–543)	FLGFLGAAGSTMGAA-SLTLTVQARC	Vaccine	Rhesus macaque( )	[Nehete1993]

Vaccine: *Vector/type:* peptide

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice, and in rhesus monkeys
- Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys

gp160(519–543)	Env(519–543)	FLGFLGAAGSTMGAA-SLTLTVQARQ	HIV-1 infection	human, chimpanzee( )	[Nehete1998a]

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env

gp160(519–543)	gp41(519–543)	FLGFLGAAGSTMGAA-SLTLTVQARC	Vaccine	murine(H-$2^{bxk,sxd}$)	[Sastry1991]

Vaccine: *Vector/type:* peptide

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160

gp160(547–561)	gp41(547–561 IIIB B10)	GIVQQQNNLLRAIEA	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(562–576)	gp41(562–576 IIIB B10)	QQHLLQLTVWGIKQL	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(572–591)	gp41(572–591)	GIKQLQARILAVERYL-KDQQ	Vaccine	murine(H-$2^{d,b}$)	[Brown1995]

Vaccine: *Vector/type:* peptide

- This peptide was a good immunogen in BALB/c and CBA mice, producing a strong proliferative response
- At least one of the four residues GIKQ enhances stimulation, and in CBA mice these residues influence the ability to prime T-cells *in vivo*
- QLQARILAVERY stimulated the greatest *in vitro* T-cell response
- VERYLKDQQ was the minimal reactive sequence recognized by a T-cell line

gp160(576–591)	gp41(576–591)	LQARILAVERYLKDQQ	Vaccine	murine(H-$2^{d,b}$)	[Brown1995]

Vaccine: *Vector/type:* peptide

- This peptide was a poor immunogen in BALB/c and CBA mice used in this experiment, producing a weak proliferative response

gp160(578–608)	gp41(585–615 IIIB)	ARILAVERYLKDQQLL-GIWGCSGKLICTTAV	Vaccine	murine( )	[Goodman-Snitkoff1990]

Vaccine: *Vector/type:* peptide

- Identification of putative Th epitopes that can stimulate an antibody response in peptide immunized mice

gp160(579–601)	gp41(579–601)	RILAVERYLKDQQLLG-GIWGCSGK	Vaccine	murine(H-$2^{d,b}$)	[Brown1995]

Vaccine: *Vector/type:* peptide

- This peptide was a good immunogen in BALB/c and CBA
- This peptide produced a strong Th response in both mice strains which was more responsive towards GIKQLQARILAVERYLKDQQ and LQARILAVERYLKDQQ than to immunizing peptide

gp160(579–604)	gp41(584–609 LAI)	RILAVERYLKDQQLLG-IWGCSGKLIC	HIV-1 infection	human( )	[Schrier1989]
• Stimulates T-cell proliferation in HIV-infected donors					
gp160(586–597)	Env(586–598)	YLRDQQLLGIWG	HIV-1 infection	human, chimpanzee( )	[Nehete1998a]
• HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env					
gp160(586–598)	Env(586–598)	YLRDQQLLGIWGC	Vaccine	murine, Rhesus macaque( )	[Nehete1993]
Vaccine: *Vector/type:* peptide					
• Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice					
• Proliferative response to this peptide was observed in 1/3 immunized rhesus monkeys, with a weak transient response in the other two					
gp160(593–604)	gp41(593–604 IIIB)	LGIWGCSGKLIC	HIV-1 infection	human( )	[Bell1992]
• Elicits T-cell proliferation and B cell responses, but only during the asymptomatic phase of HIV infection					
gp160(593–604)	gp41(598–609 LAV-1)	LGLWGCSGKLIC	Vaccine	murine($H2^d$)	[Schrier1988]
• Murine T-dependent B-cell response – 7/29 had a proliferative response to this peptide					
gp160(594–603)	gp41(594–603 IIIB)	GIWGCSGKLI	HIV-1 infection	human( )	[Kelleher1998]
• Epitope documented as a "previously described" epitope [Bell1992], but in Bell *et al.* it was described as gp41(594-603 IIIB), LGIWGCSGKLIC					
• Immunization with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre					
• Immunization with p24-VLP did not increase the proliferative response to this gp41 epitope, however, there was a modest, short-lived increased proliferative response to p24					
gp160(594–604)	gp41( )	GIWGCSGKLIC	HIV-1 infection	human( )	[Mutch1994]
• Core region of peptides that can stimulate proliferative responses from seronegative and seropositive people					
gp160(598–609)	gp41(603–614 LAI)	CSGKLICTTAVP	HIV-1 infection	human( )	[Schrier1989]
• Stimulates T-cell proliferation in HIV-infected donors					
gp160(604–615)	gp41(609–620 LAI)	CTTAVPWNASWS	HIV-1 infection	human( )	[Schrier1989]
• Stimulates T-cell proliferation in HIV-infected donors					

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
gp160(606–620)	gp41( )	TNVPWNASWSNKSLE	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This gp140 epitope of UG92005 (UG, clade D) was recognized by five hybridomas with Vβ usage Vβ 8.1, 14 and not determined – one of the Vβ 8.1 was shown to utilize Vα 8
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

gp160(609–616)	gp41( )	PWNASWSN	HIV-1 infection	human( )	[Mutch1994]

- Core region of peptides that can stimulate proliferative responses from seronegative and seropositive people

gp160(611–620)	gp41( )	NASWSNKSLE	Vaccine	murine(H-2 IA^b)	[Surman2001]

Vaccine: *Vector/type:* DNA, vaccinia, recombinant protein *Strain:* 1007 (clade B), UG92005 (clade D) *HIV component:* gp140 *Stimulatory Agents:* Freund's adjuvant

- This gp41 epitope is conserved in 1007 (US, clade B) and UG92005 (UG, clade D) and was recognized by two hybridomas from two different mice that were vaccinated with different clades – the Vβ usage was Vβ 4 and 14
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (T[TN]VPWNASWSNKSLE and NASWSNKSLEQIWNN) – the only difference between 1007 and UG92005 for these two proteins is that 1007 has a T and UG92005 has an N in the second position of the first peptide
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells

- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D strain isolated from Uganda in 1992 through the WHO
- 80 unique clonotypes were characterized from six mice
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23in V4C4, and 7 in gp41
- Epitopes hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein – the non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways

gp160(614–629)	gp41( )	WSNKSLEDIWDNMTW-C	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

gp160(634–649)	gp41( )	EIDNYTNTIYTLLEEC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

gp160(647–661)	gp41(647–661 IIIB B10)	EESQNQQEKNEQELL	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(650–662)	gp41(655–667 LAI)	QNQQEKNEQELLE	HIV-1 infection	human( )	[Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

gp160(667–681)	gp41(667–681 IIIB B10)	ASLWNWFNITNWLWY	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(682–696)	gp41(682–696 IIIB B10)	IKLFIMIVGGLVGLR	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

gp160(724–745)	gp41(731–752)	PRGPDRPEGIEEEGGE-RDRDRS	Vaccine	murine(H-2k)	[McInerney1999]

Vaccine: *Vector/type:* peptide in cowpea mosaic virus (CPMV) *HIV component:* gp41 *Stimulatory Agents:* adjuvant Quil A

- A gp41 peptide was expressed in a cowpea mosaic virus (CPMV) and mice were vaccinated with a purified chimeric particle – out of five adjuvants tested, only Quil A could stimulate anti-gp41 antibodies and an *in vitro* proliferative response

- The antibodies were predominantly IgG2a, suggesting a Th1 response

gp160(732–744)	gp41(737–749 LAI)	GIEEEGGERDRDR	HIV-1 infection	human( )	[Schrier1989]

- Stimulates T-cell proliferation in HIV-infected donors

gp160(780–794)	gp160(787–801 IIIB)	RIVELLGRRGWEALK	Vaccine	murine(H-2^k, H-2^d, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), and B10.S(9R) mice (H-2A^s, E^s)
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including RIVELLGRRGWEALK and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2^k mice

gp160(780–794)	gp41(787–801 IIIB)	RIVELLGRRGWEALK	Vaccine	murine(H-2^{d,k,t4})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

gp160(780–813)	gp160(787–820 IIIB)	RIVELLGRRGWEALK-YWWNLLQYWSQELKNS-AVS	HIV-1 infection, Vaccine	murine(H-2^k)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people
- This cluster peptide elicited proliferative responses in cells from only B10.BR mice (H-2A^k, E^k), and not from B10.D2 mice (H-2A^d, E^d), B10.A(5R) mice (H-2A^b, E^b), or B10.S(9R) mice (H-2A^s, E^s)
- IL-2 production in response to this peptide was observed in 59% (17/29) of asymptomatic HIV-infected individuals

gp160(794–808)	gp160(801–815 IIIB)	KYWWNLLQYWSQELK	Vaccine	murine(H-2^k, H-2^d, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), and B10.S(9R) mice (H-2A^s, E^s)
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including KYWWNLLQYWSQELK and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2^k mice

gp160(794–808)	gp41(801–815 IIIB)	KYWWNLLQYWSQELK	Vaccine	murine(H-2^k)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(799–813)	gp160(806–820 IIIB)	LLQYWSQELKNSAVS	Vaccine	murine(H-2^k, H-2^d, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), and B10.S(9R) mice (H-2A^s, E^s)
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including LLQYWSQELKNSAVS and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2^k mice

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gp160(799–813)	gp41(806–820 IIIB)	LLQYWSQELKNSAVS	Vaccine	murine(H-$2^{k,d,t4}$)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(799–813)	gp41(806–820 IIIB)	LLQYWSQELKNSAVS	Vaccine	murine(H-$2^{k,d,t4}$)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(814–829)	gp41( )	WLNATAIAVTEGTDRC	*in vitro* stimulation	human( )	[Manca1995b]

- Peptide stimulation of PBMC from non-infected individuals *in vitro*
- Peptide priming does not always induce T-cells that recognize whole protein

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gp160(821–835)	gp160(828–842 IIIB)	AVAEGTDRVIEVVQG	Vaccine	murine(H-2^k, H-2^b, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)
- AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER encompasses several murine Th epitopes including AVAEGTDRVIEVVQG and is referred to as a "multideterminant region" or cluster peptide

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gp160(821–835)	gp41(828–842 IIIB)	AVAEGTDRVIEVVQG	Vaccine	murine(H-2^k)	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(821–838)	gp41(827–843)	YVAEGTDRVIEVVQG-ACR	HIV-1 infection	human( )	[Caruso1997]

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24

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gp160(821–853) gp160(828–860 IIIB) AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER HIV-1 infection, Vaccine human, murine(H-2^k, H-2^b, H-2^s, H-2^d) [Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide
- Six multideterminant region cluster peptides were evaluated for Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people
- This cluster peptide elicited proliferative responses in cells from all four MHC types tested: B10.BR mice (H-$2A^k$, E^k), B10.D2 mice (H-$2A^d$, E^d), B10.A(5R) mice (H-$2A^b$, E^b), and B10.S(9R) mice (H-$2A^s$, E^s)
- IL-2 production in response to this peptide was observed in only 8% (1/12) of asymptomatic HIV-infected individuals

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gp160(827–835) gp41(834–842 IIIB) DRVIEVVQG Vaccine murine(H-2^k) [Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Suggested epitope based on region of overlap

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR Vaccine Rhesus macaque( ) [Hosmalin1991]

Vaccine: *Vector/type:* peptide prime with protein boost *Strain:* IIIB *HIV component:* gp160

- Epitope name: TH4. Peptide priming to induce T-cell help enhances antibody response to gp160 immunization
- Called Th4.1 and TH4

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 infection human( ) [Clerici1997]

- Epitope name: TH4. Used in a study of the influence of pentoxifylline on HIV specific T-cells

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 exposed seronegative human( ) [Pinto1995a]

- Epitope name: TH4. CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers
- Called Th4.1 and TH4

---

gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 infection human( ) [Clerici1991a]

- Epitope name: TH4. Peptides stimulate Th cell function and CTL activity in similar patient populations
- Called Th4.1 and TH4

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR Vaccine human( ) [Clerici1991b]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160

- Epitope name: TH4. Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection
- Called Th4.1 and TH4

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 exposed seronegative human( ) [Clerici1992]

- Epitope name: TH4. Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men
- Called Th4.1 and TH4

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 infection human( ) [Clerici1989]

- Epitope name: TH4. IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals
- Called Th4.1 and TH4

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 infection human( ) [Kaul1999a]

- Epitope name: TH4. Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- The helper epitopes used in this study were noted to be previously described [Clerici1989], and were not explicitly described in [Kaul1999a]

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gp160(827–841) gp41( ) DRVIEVVQGAYRAIR HIV-1 exposed seronegative, HIV-1 infection human( ) [Kuhn2001]

- Epitope name: TH4, Th4.1. In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL-2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4
- The mothers were predominantly infected subtype C but the T-helper response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents
- 3/33 infants with cord blood T-helper responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected – 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding
- Measurable HIV specific T-helper responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1

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gp160(827–841) gp160(834–848 IIIB) DRVIEVVQGAYRAIR Vaccine murine(H-2^{k}, H-2^{b}) [Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^{k}, E^{k}) and B10.A(5R) mice (H-2A^{b}, E^{b})

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR Vaccine murine(H-2^{k,i5}) [Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Epitope name: TH4. Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types
- Called Th4.1 and TH4

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gp160(829–837)	gp160(836–850 IIIB)	VIEVVQGAYRAIRHI	Vaccine	murine(H-2^k, H-2^b)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k) and B10.A(5R) mice (H-2A^b, E^b)

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gp160(834–841)	gp41(841–848 IIIB)	QGAYRAIR	Vaccine	murine(H-2^{i5})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Suggested H-2^k epitope based on region of overlap

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gp160(834–848)	gp160(841–855 IIIB)	QGAYRAIRHIPRRIR	Vaccine	murine(H-2^k, H-2^b, H-2^d, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.A(5R) mice (H-2A^b, E^b), B10.D2(H-2A^d, E^d), and B10.S(9R) mice (H-2A^s, E^s)

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gp160(834–848)	gp41(841–855 IIIB)	QGAYRAIRHIPRRIR	Vaccine	murine(H-2^{d,t4,i5})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(839–848)	gp41(846–855 IIIB)	AIRHIPRRIR	Vaccine	murine(H-2^{d,t4})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Suggested H-2^{d,t4} epitope based on region of overlap

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gp160(839–853)	gp160(828–842 IIIB)	AIRHIPRRIRQGLER	Vaccine	human, murine(H-2^k, H-2^b, H-2^s)	[Berzofsky1991, Berzofsky1991a]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* Freund's adjuvant

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)

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gp160(839–853)	gp41(846–860 IIIB)	AIRHIPRRIRQGLER	Vaccine	murine(H-2^{d,t4})	[Hale1989]

Vaccine: *Strain:* IIIB *HIV component:* gp160

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types

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gp160(842–856)	gp41(842–856 IIIB B10)	HIPRRIRQGLERILL	HIV-1 infection	human( )	[Wahren1989, Wahren1989a]

- 12 gag and 18 env T-cell sites were identified that could commonly evoke T-cell responses

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Table 14: **Env**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Env( )	gp120( )		Vaccine	murine( )	[Shiver1997b]
Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp120, gp160					
• DNA vaccinations of BALBc mice with a gp120 or gp160 DNA vaccine elicited a strong T-cell proliferative response with Th1-like secretion of γ interferon and IL-2, with little or no IL-4, as well as antigen specific gp120 Abs • An intramuscular route of inoculation gave a stronger proliferative response than intradermal • A proliferative response could be detected in all lymph tissues tested: spleen, PBMC, and mesenteric, iliac, and inguinal lymph nodes					
Env( )	gp120( )		Vaccine	murine( )	[Kim1997f]
Vaccine: *Vector/type:* DNA *HIV component:* gp160, Gag, Pol *Stimulatory Agents:* CD86 expression vector					
• A gp160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecule CD86, gives an increase in the proliferative responses to gp120 in mice					
Env( )	gp120( )			human( )	[DeBerardinis1997]
• Sequences flanking helper T-cell immunogenic domains can be important for immunogenicity					
Env( )	gp120( )	polyclonal	HIV-1 infection	human( )	[Rosenberg1997]
• A strong proliferative response to p24 and gp160 was found in a healthy long term survivor					
Env( )	gp120( )	polyclonal	HIV-1 infection	Macaca nemestrina( )	[Kent1997c]
• Macaca nemestrina can be infected with HIV, and clear the infection within 6 months, so it is of interest to examine their initial immune response • A strong proliferative response against gp160 with IL-4 production, indicating a Th2 response, was found with 4 weeks of infection • The gp160 proliferative response by 8 weeks produces both IL-4 and γ interferon, indicating both Th1 and Th2 responses					
Env( )	gp120( )	polyclonal	Vaccine	Rhesus macaque( )	[Letvin1997b]
Vaccine: *Vector/type:* DNA prime with rgp160 boost *Strain:* HXBc2 *HIV component:* gp160					
• Vaccination of Macaca mulatta (rhesus monkeys) with a HXBc2 env DNA prime and a protein boost elicited a T-cell proliferative response, a CTL response, and type-specific neutralizing antibodies • Vaccinated animals challenged with SHIV-HXB2 were protected from infection					
Env( )	gp120( )	polyclonal	HIV-1 infection, Vaccine	human( )	[MacGregor1998b]
Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* Env, Rev					
• An HIV DNA env and rev vaccine given to 15 asymptomatic HIV+ individuals at three different dosages, 30, 100 or 300 μg, was safe • All three groups showed an increased proliferative response after vaccination					

Env( )	Env( )	HIV-1 exposed seronegative	human( )	[Mazzoli1997]

- Study of HIV-specific immunity in seronegative partners of HIV-positive individuals – Env peptides could stimulate IL-2 production in 9/16 HIV-exposed seronegative individuals, and only 1/50 low-risk controls
- Exposed-uninfected produced more IL-2 and less IL-10 than HIV-infected individuals
- 8/9 of those whose PBMC produce IL-2 in response to Env peptides had concomitantly detected urinary or vaginal tract anti-HIV IgA

Env( )	Env( )	HIV-1 infection	human( )	[Plana1998]

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses

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Env( )	Env( )	HIV-1 infection	human( )	[Kelleher1998a]

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL-2 therapy – while IL-2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses

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Env( )	gp160( )	HIV-1 infection, Vaccine	human( )	[Ratto-Kim1999]

Vaccine: *Vector/type:* recombinant protein *HIV component:* gp160

- Vaccinations with rgp160 did not enhance Th immunoproliferative responses in individuals who were immunized every 2 months for 5 years starting early in infection

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Env( )	gp160( )	HIV-1 infection, Vaccine	human( )	[Leandersson2000]

Vaccine: *Vector/type:* recombinant protein *HIV component:* gp160

- 27 HIV subtype B, 4 subtype C, 2 D and one of each subtype E, F, G were either given rgp160 B clade immunizations or placebo – all rgp160 immunized individuals showed increased proliferation responses to the B clade immunizing antigen rgp160
- gp120 was prepared from A, B, C, D, and E subtype virions and used as antigenic stimulus – 7 of 10 tested individuals responded to native gp120 from at least one additional subtype in addition to B subtype, while a placebo recipient did not respond to any gp120
- This study shows that cross-subtype HIV-specific T-cell proliferative responses can be stimulated in patients already infected with another HIV-1 subtype – all immunized subjects could respond to the subtype B immunogen, but many developed responses to at least one more subtype

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Env( )	gp160( )	Vaccine	human( )	[Gorse1999a]

Vaccine: *Vector/type:* gp160 prime with gp120 boost *Strain:* MN *HIV component:* gp160, gp120

- Helper T-cell memory responses were induced by MN rgp160 as measured by proliferation and Th1 and Th2 cytokine release – this response could be boosted by MN rgp120

Env( )	gp120( )	Vaccine	Rhesus macaque( )	[Heeney1998]

Vaccine: *Vector/type:* ISCOM or fowlpoxvirus *Strain:* SF2 *HIV component:* gp120

- Vaccinated monkeys with the highest level of Th1 and Th2 responses and the highest levels of NAbs were protected against a SHIV SF13 challenge – the ISCOM strategy gave more potent anti -gp120 responses than the Fowl pox strategy
- When animals were challenged 4 months after boost, those that maintained high levels of HIV-1 specific IFN-γ responses, indicative of a Th1 response, were still protected

Env( )	( )	HIV-1 infection, Vaccine	human( )	[Boyer1999]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* Env, Rev

- A DNA vaccine containing env and rev was tested for safety and immune response in 15 HIV+ asymptomatic individuals
- Enhanced proliferative activity and higher levels of MIP-1α were detected in multiple study subjects

Env( )	Env( )	Vaccine	murine BALB/c( )	[Rodriguez1999]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* GM-CSF-Env chimera

- A chimeric GM-CSF-Env antigen expressed in a vaccinia vector elicits a higher HIV-specific Env cellular immune response than when native Env is used

Env( )	Env( )	Vaccine	Macaca nemestrina( )	[Kent1998a]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *Strain:* LAI *HIV component:* Env, Gag

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T-helper response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced

Env( )	gp120( )	Vaccine	Rhesus macaque( )	[Heeney1999b]

Vaccine: *Vector/type:* DNA, protein, virus-like particle, ISCOM

- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge. Protection correlated with the magnitude of NAb responses, β-chemokines, and a balanced Th response. DNA, protein+adjuvant, VLP and ISCOM vaccines were tested.
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced β-chemokine production

Env( )	gp160( )	HIV-1 infection, Vaccine	human( )	[Kundu1998c]

Vaccine: *Vector/type:* protein *Strain:* MN *HIV component:* gp160

- This study followed 10 HLA-A2 asymptomatic HIV+ individuals as they received MN gp160 vaccinations over a two year period.
- There was an increased lymphoproliferative response but this did not impact viral load or CTL response

Env( )	gp120( )	Vaccine	Rhesus macaque( )	[Verschoor1999]

Vaccine: *Vector/type:* DNA, recombinant protein, ISCOM *Strain:* SF2 *HIV component:* gp120 *Stimulatory Agents:* Adjuvant MF59

- 16 rhesus Macaques were vaccinated with either an epidermal SF2 gp120 DNA vaccine, rgp120 with a MF59 adjuvant, or rgp120 incorporated into ISCOMs

- DNA vaccination elicited a weak Th type 1 response and low antibody response, rgp120/MF59 triggered a strong antibody response, and rgp120/ISCOM induced both kinds of Th cells, and a strong humoral response.
- Animals were challenged with SF13 SHIV. Early induction of Th type 1 and type 2 responses with the rgp120/ISCOM vaccine provided the most effective immunity, protecting from infection

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Env( ) Env( ) Vaccine murine( ) [Kim1998d]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* Gag, Pol, Env *Stimulatory Agents:* CD80 and CD86 expression vectors

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Env( ) Env( ) Vaccine human( ) [Salmon-Ceron1999a]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers

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Env( ) Env( ) Vaccine Rhesus macaque( ) [Akahata2000]

Vaccine: *Vector/type:* DNA *Strain:* ZF1 *HIV component:* complete genome

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected
- PBMC from all vaccinated monkeys produced IFNγ, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit

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Env( ) gp120( ) HIV-1 infection human( ) [Zhang2001]

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient

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Env( ) gp160( ) HIV-1 infection human( ) [Blazevic2000]

- Prolonged viral suppression resulting from potent anti-retroviral therapy did not allow an HIV T-helper response increase to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients

---

Env( ) gp120( ) HIV-1 infection human( ) [Oxenius2000b]

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable

---

Env( ) gp120( ) Vaccine human( ) [Sabbaj2000]

Vaccine: *Vector/type:* canarypox prime with rgp120 boost *HIV component:* gp120

- Proliferative responses in PBMC of uninfected individuals that were vaccinated with canarypox vector expressing HIV-1 antigens (ALVAC-HIV) and boosted with a recombinant gp120 subunit vaccine gave a Th1 and Th2 proliferative response upon stimulation with HIV-1 Env
- All vaccinees produced IFNγ and IL110, most also produced IL-2, IL-6, IL-4 and IL-5

Env( ) gp120( ) Vaccine murine(H-2^d) [Kim2000a]

Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Env *Stimulatory Agents:* IL-2, IL-4 and IFNγ expression vectors

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of Th1 cytokine IFN-γ drove Th1 immune responses and enhanced CTL responses

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Env( ) gp120( ) Vaccine murine(H-2^d) [Shirai2001]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Helicobacter pylori induces Th1 responses early, but predominantly Th2 responses later in infection (at 6 weeks) – differentiation of HIV-1 gp160 CD4+ help and CD8+ CTL effector cells in response to HIV gp160-vaccinia vaccination is impaired in BALB/c mice infected with H. pylori

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Env( ) gp160( ) Vaccine murine(H2^d) [Morris2000a]

Vaccine: *Vector/type:* peptide, recombinant protein *Strain:* IIIB *HIV component:* gp160, V3 *Stimulatory Agents:* Adjuvant LT(R192G)

- Mice were intranasally immunized with 20 ug of HIV-gp160 and 5 ug of peptide E7 (RIHIGPGRAFYAARK) with the adjuvant LT(R192G), a heat-labile enterotoxin produced by *E. coli*
- Adjuvant LT(R192G) was required for stimulation of antigen-specific IgG1, IgG2 antibodies, and Th1 and Th2 cytokines responses to gp160, and peptide-specific CTL responses
- Increased IFN-γ, IL-10 and IL-6 cytokine production specific to gp160 was measured with co-immunization of gp160 with LT(R192G)

Env( ) gp160( ) Vaccine murine(H2^d) [Arai2000a]

Vaccine: *Vector/type:* DNA, CMV promotor *Strain:* IIIB *HIV component:* gp160, Rev *Stimulatory Agents:* Br-cAMP

- The CMV promotor responds to the intracellular level of cAMP, and 8 Br-cAMP can increase transgene expression so it was co-administered with a CMV-based DNA vaccine both intranasally and intramuscularly
- 8 Br-cAMP increased serum IgG responses, HIV-specific CTL, DTH and Th1 responses, and IgA in the intranasal vaccination
- A CAT assay study showed adjuvant effect was due to CMV promotor activation

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Table 15: **Nef**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Nef(1–20)	Nef(1–20 LAI)	MGGKWSKSSVVGWPT-VRERM	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Nef(16–35)	Nef(16–35 LAI)	VRERMRRAEPAADGV-GAASR	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Nef(31–50)	Nef(31–50 LAI)	GAASRDLEKHGAITSS-NTAA	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Nef(45–69)	Nef(45–69 BRU)	SSNTAATNAACAWLE-AQEEEEVGFP	Vaccine	rat, chimpanzee( )	[Estaquier1992]
Vaccine: *Vector/type:* peptide prime with protein boost *Strain:* BRU *HIV component:* Nef • Antigenic domain: ATNAACAWL, priming with peptide enhanced subsequent Ab response to Nef protein immunization					
Nef(46–65)	Nef(46–65 LAI)	SNTAATNAACAWLEA-QEEEE	Vaccine	murine(H-2^d)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein • Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev					
Nef(61–80)	Nef(61–80 LAI)	QEEEEVGFPVTPQVPL-RPMT	Vaccine	murine(H-2^b)	[Hinkula1997]
Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev • Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein					

- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(66–97)	Nef(66–97 LAI)	VGFPVTPQVPLRPMT-YKAAVDLSHFLKEKGG-L	Vaccine	human( )	[Gahery-Segard2000a]

Vaccine: *Vector/type:* lipopeptide

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 5/10 reacted to this Nef peptide
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual
- 5/12 tested had an IgG response to this peptide

Nef(76–95)	Nef(76–95 LAI)	LRPMTYKAAVDLSHF-LKEKG	Vaccine	murine(H-2^b)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(91–110)	Nef(91–110 LAI)	LKEKGGLEGLIHSQRR-QDIL	Vaccine	murine(H-2^b)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(98–112)	Nef(98–112 BRU)	EGLIHSQRRQDILDL	Vaccine	chimpanzee( )	[Estaquier1992]

Vaccine: *Vector/type:* peptide prime with protein boost *Strain:* BRU *HIV component:* Nef

- Peptide alone could stimulate chimpanzee T-cells in the absence of carrier protein – required carrier protein in rat

Nef(104–123)	Nef(106–125 HXB3)	QRRQDILDLWIYHTQ-GYFPD?	Vaccine	murine(H-2^b)	[Sandberg2000]

Vaccine: *Vector/type:* DNA *Strain:* HXB3 *HIV component:* Nef

- A strong T-helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes

Nef(106–125)	Nef(106–125 LAI)	RQDILDLWIYHTQGYF-PDWQ	Vaccine	murine(H-2^b)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(117–147)	Nef(117–147 LAI)	TQGYFPDWQNYTPGP-GVRYPLTFGWCYKLVP	Vaccine	human( )	[Gahery-Segard2000a]

Vaccine: *Vector/type:* lipopeptide

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 1/10 reacted to this Nef peptide
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual
- 10/12 tested had an IgG response to this peptide

Nef(121–140)	Nef(121–140 LAI)	FPDWQNYTPGPGVRY-PLTFG	Vaccine	murine(H-2^b)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(136–155)	Nef(136–155 LAI)	PLTFGWCYKLVPVEPD-KVEE	Vaccine	murine(H-2^d)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(151–170)	Nef(151–170 LAI)	DKVEEANKGENTSLL-HPVSL	Vaccine	murine(H-2^d)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

Nef(164–183)	Nef(166–185 HXB3)	LLHPVSLHGMDDPER-EVLEW?	Vaccine	murine(H-2^b)	[Sandberg2000]

Vaccine: *Vector/type:* DNA *Strain:* HXB3 *HIV component:* Nef

- A strong T-helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes

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Nef(166–185)	Nef(166–185 LAI)	HPVSLHGMDDPEREV-LEWRF	Vaccine	murine(H-$2^{b,d}$)	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

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Nef(179–203)	Nef(181–205 HXB3)	EVLEWRFDSRLAFHH-VAREL?	Vaccine	murine(H-2^{b})	[Sandberg2000]

Vaccine: *Vector/type:* DNA *Strain:* HXB3 *HIV component:* Nef

- A strong T-helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes

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Nef(181–205)	Nef(181–205 LAI)	LEWRFDSRLAFHHVA-RELHPEYFKN	Vaccine	murine(H-2^{d})	[Hinkula1997]

Vaccine: *Vector/type:* DNA *Strain:* LAI *HIV component:* Nef, Tat, Rev

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev

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Nef(182–205)	Nef(182–205 LAI)	EWRFDSRLAFHHVAR-ELHPEYFKN	Vaccine	human( )	[Gahery-Segard2000a]

Vaccine: *Vector/type:* lipopeptide

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 4/10 reacted to this Nef peptide
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual
- None of the 12 tested had an IgG response to this peptide

Nef(185–200)	Nef(183–198)	FDSRLAFHHVARELHP	HIV-1 infection	human( )	[Ranki1997]

- T-cell response to this epitope persisted after seroreversion

Nef( )	Nef( )	HIV-1 infection	human( )	[daSilva1998a]

- This study compares the level of variation in Nef CTL epitopes to helper and MAb epitopes from the same region
- CTL epitopes tend to be more conserved than either helper or MAb epitopes and there are stronger functional constraints in the regions where CTL epitopes cluster

Nef( )	Nef( )	Vaccine	human( )	[Calarota1999a]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev Tat

- Nine HIV-1+ subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination

Nef( )	Nef( )	HIV-1 infection, Vaccine	human( )	[Calarota2001]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev, Tat *Stimulatory Agents:* CpG motifs

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals

Nef( )	Nef( )	HIV-1 infection	human( )	[Oxenius2000b]

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable

Nef( )	Nef( )	Vaccine	murine(H-2^d)	[Ayyavoo2000a]

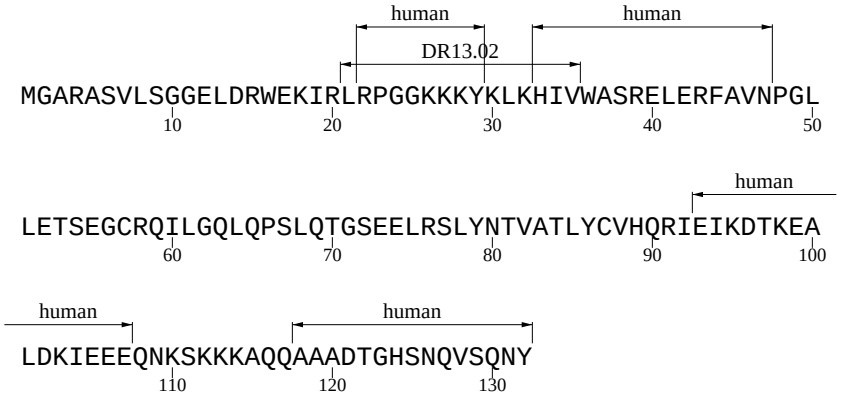
Vaccine: *Vector/type:* DNA *HIV component:* Vif, Vpu, Nef

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels
- Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response
- IL-4 production was not significantly changed after antigen stimulation compared to control levels
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell

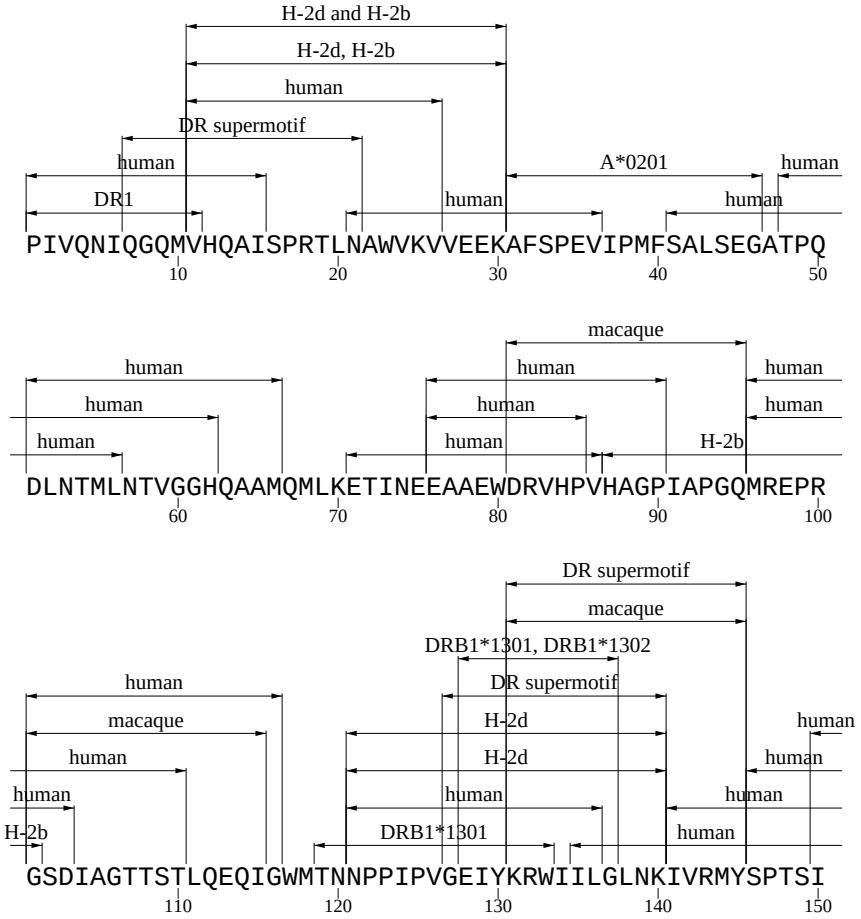
Part III-B: Maps of Helper Epitope Locations Plotted by Protein

Only epitopes <22 amino acids long are shown. If HLA specificity was not determined but the Helper T-cell response was in a person, the reactive peptide is listed as "human", otherwise the HLA presenting molecule is noted. The non-human Helper T-cell responses have the organism listed.

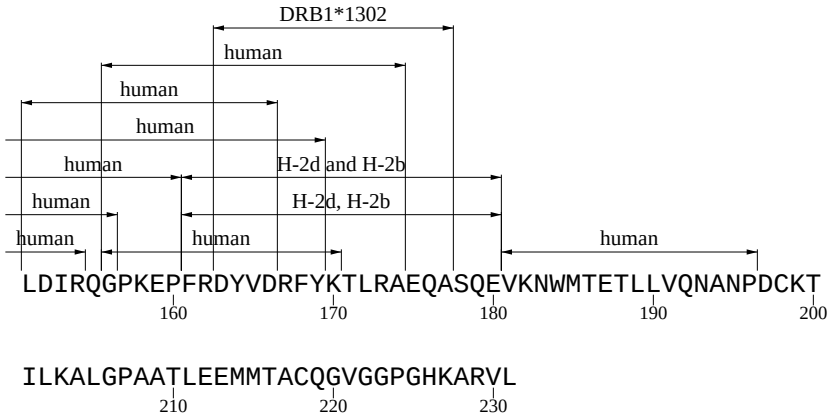
p17 Helper Map

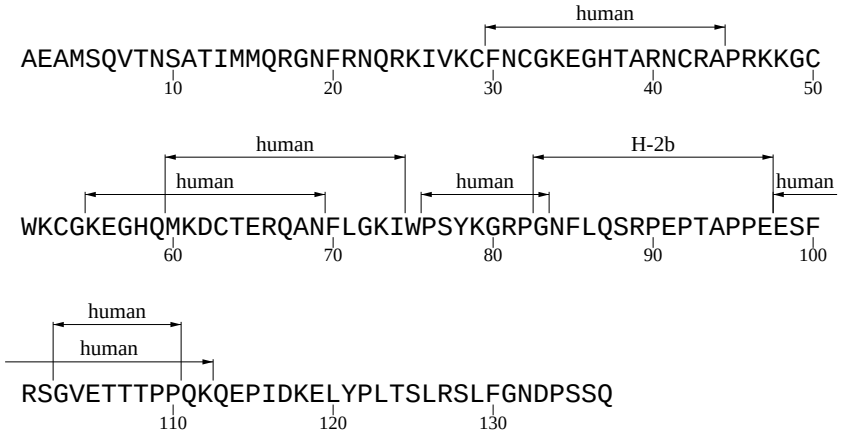


p24 Helper Map



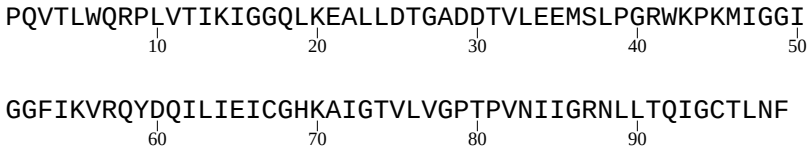
p2p7p1p6 Helper Map



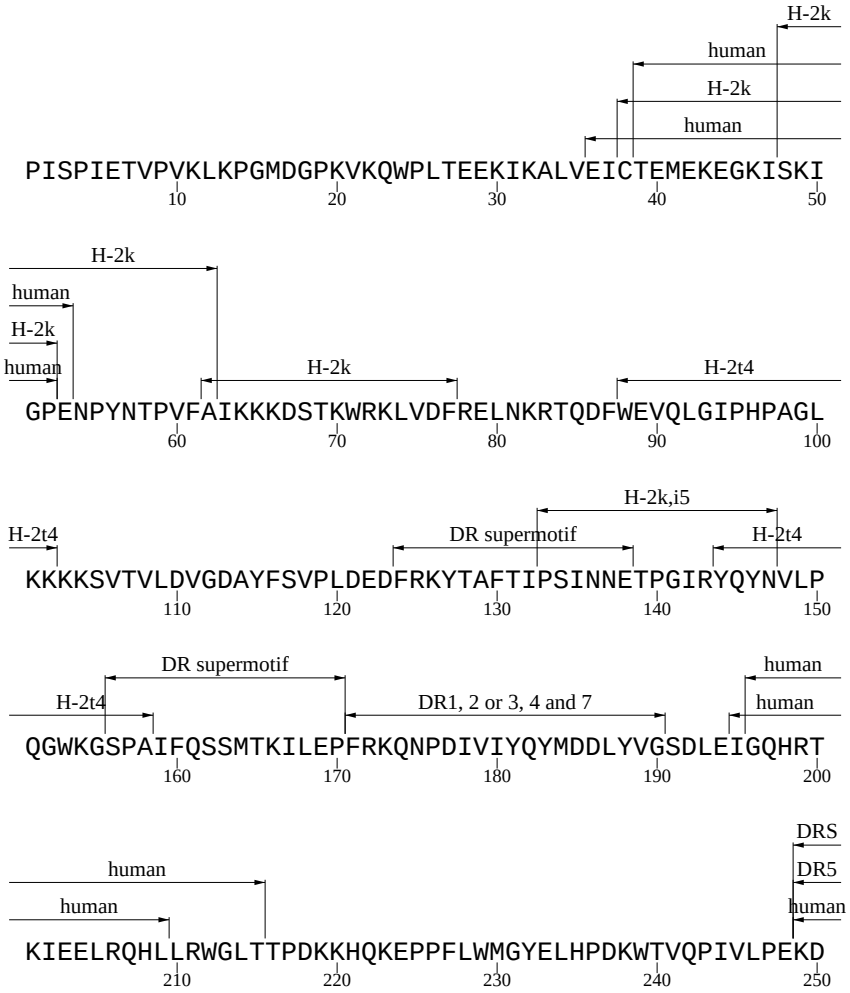


Helper T

Protease Helper Map

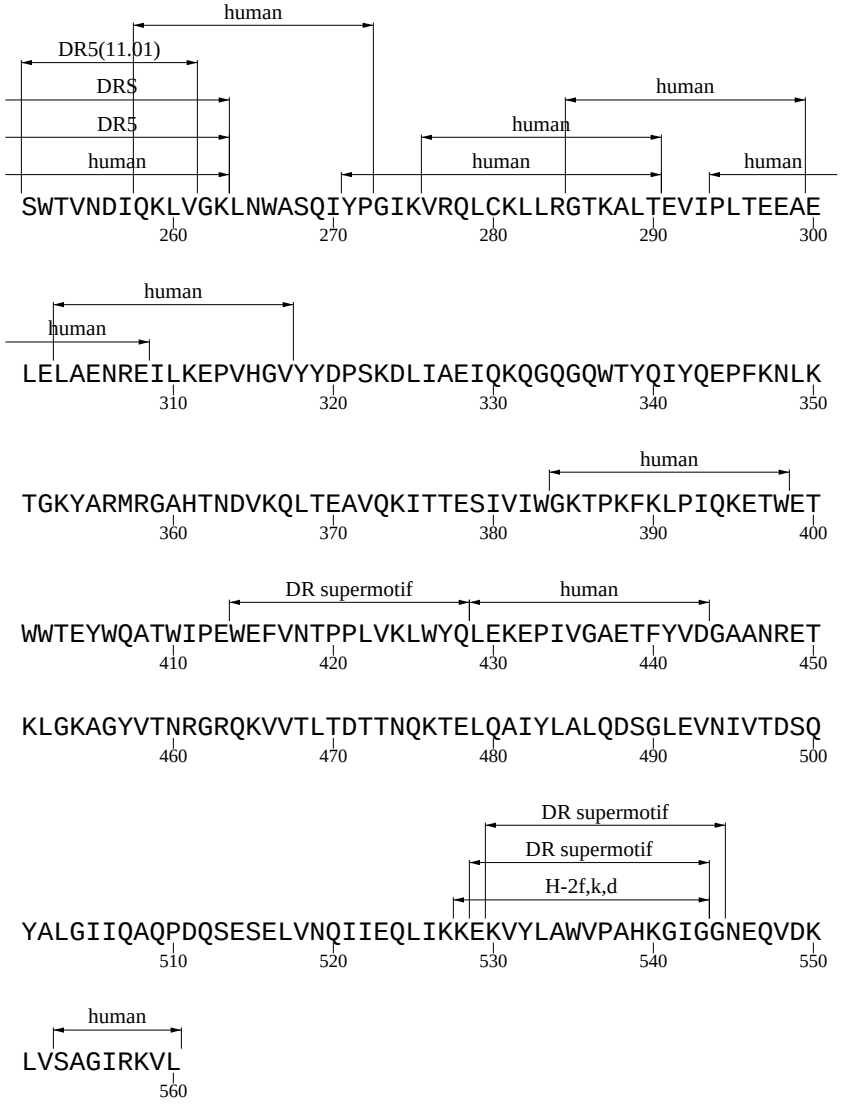


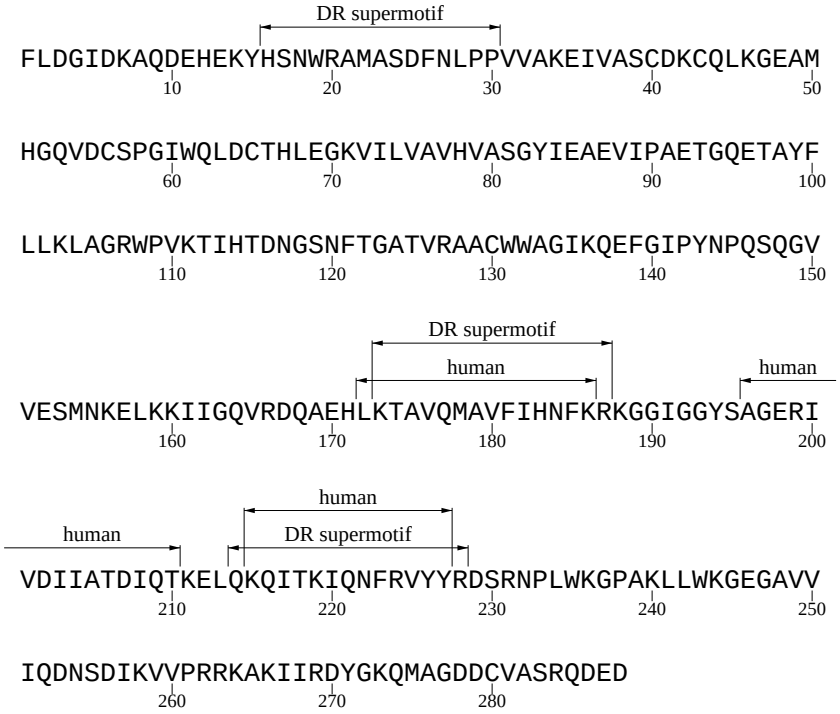
RT Helper Map



Helper T

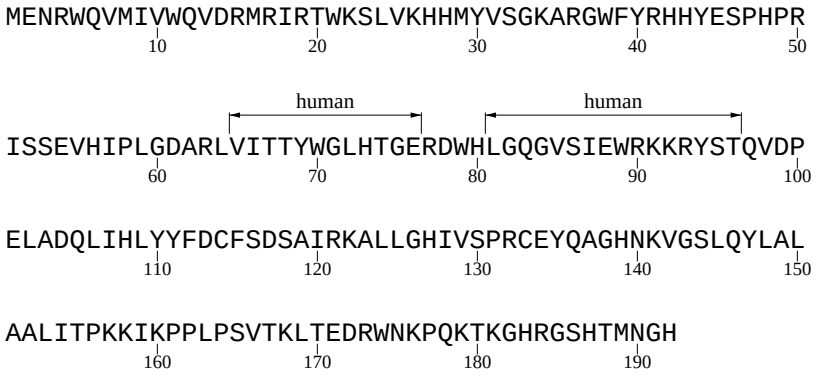
Integrase Helper Map



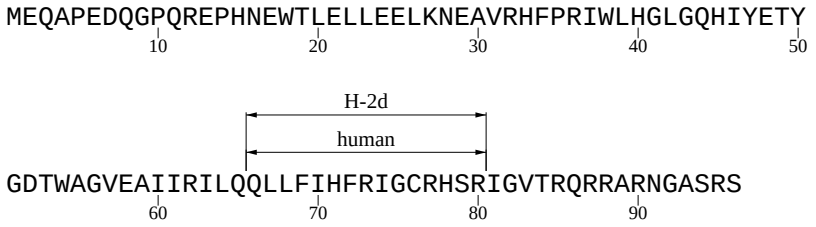


Helper T

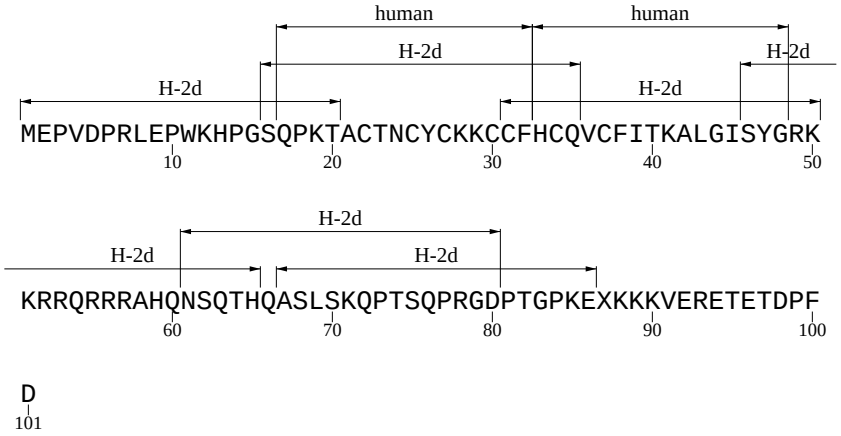
Vif Helper Map



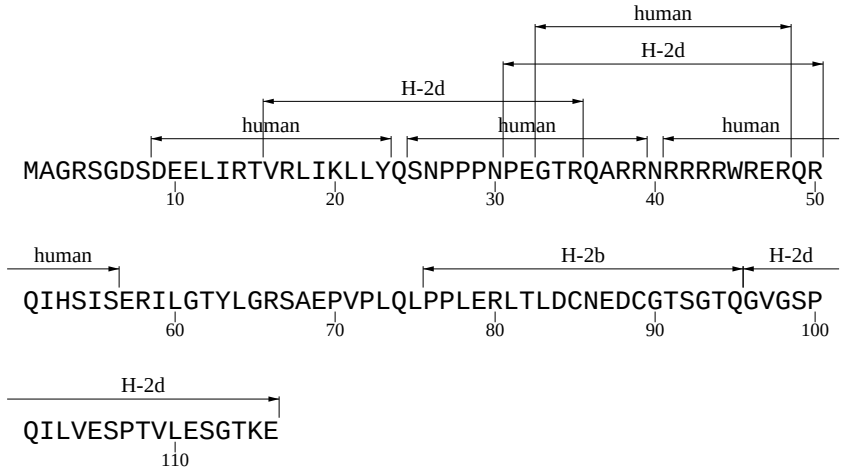
Vpr Helper Map



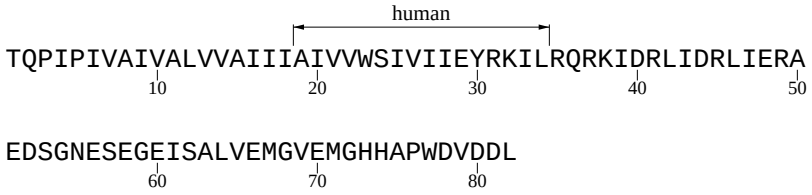
Tat Helper Map



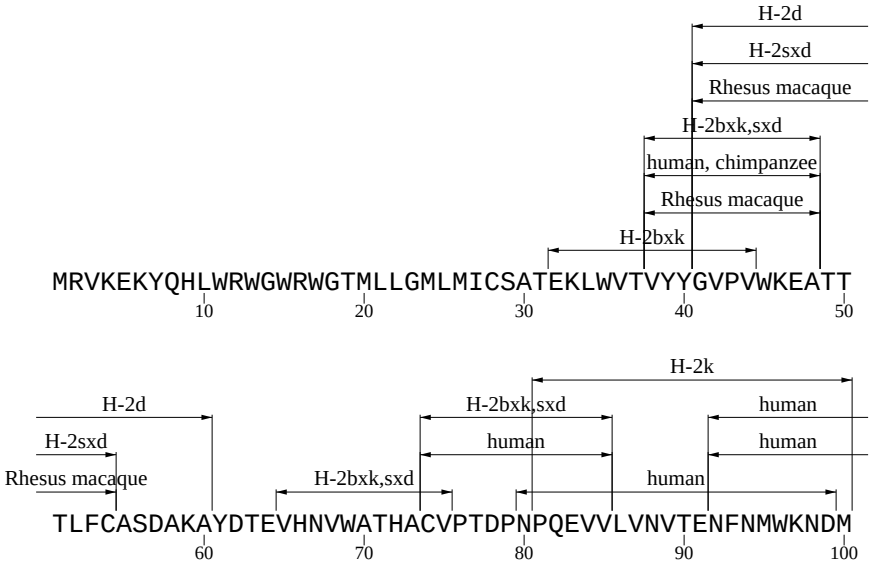
Rev Helper Map

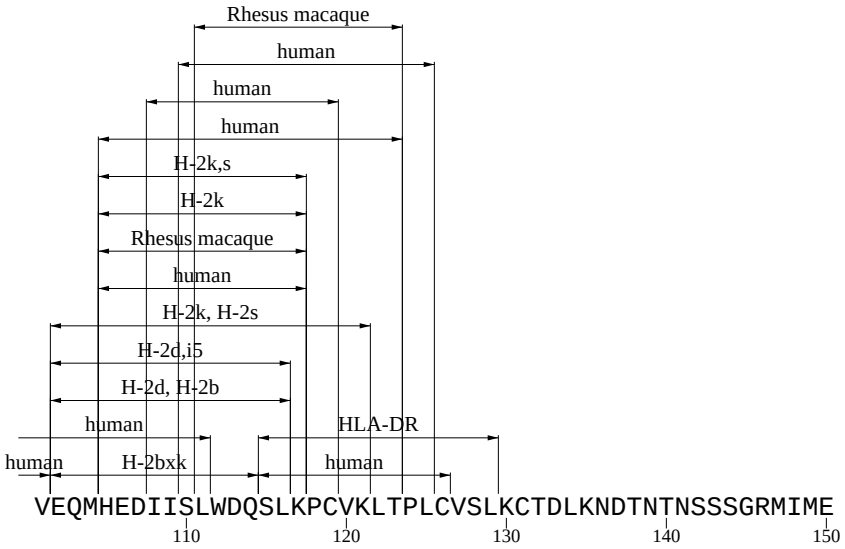


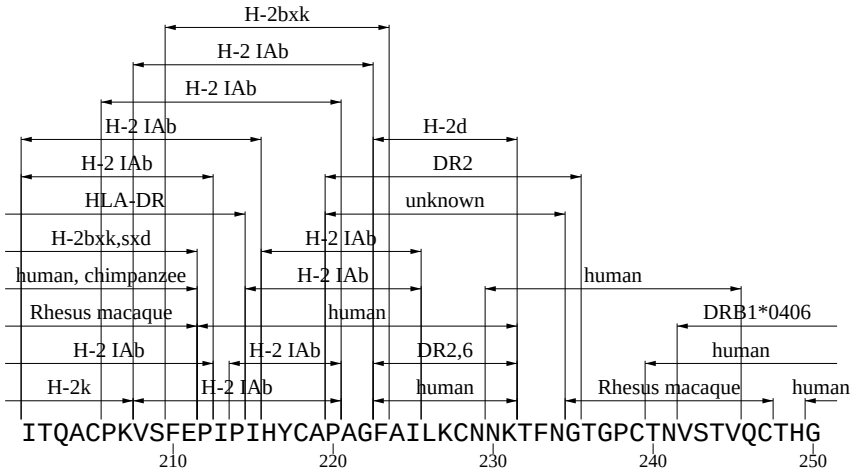
Vpu Helper Map

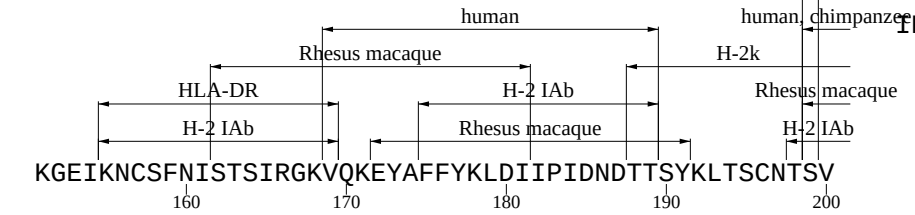


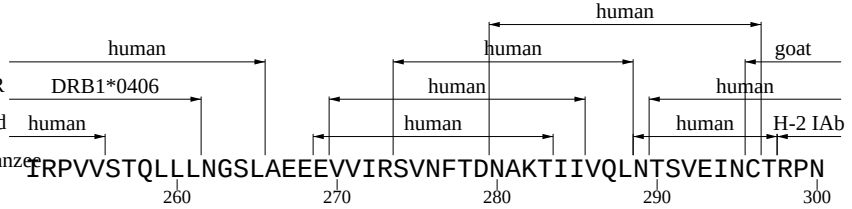
gp160 Helper Map



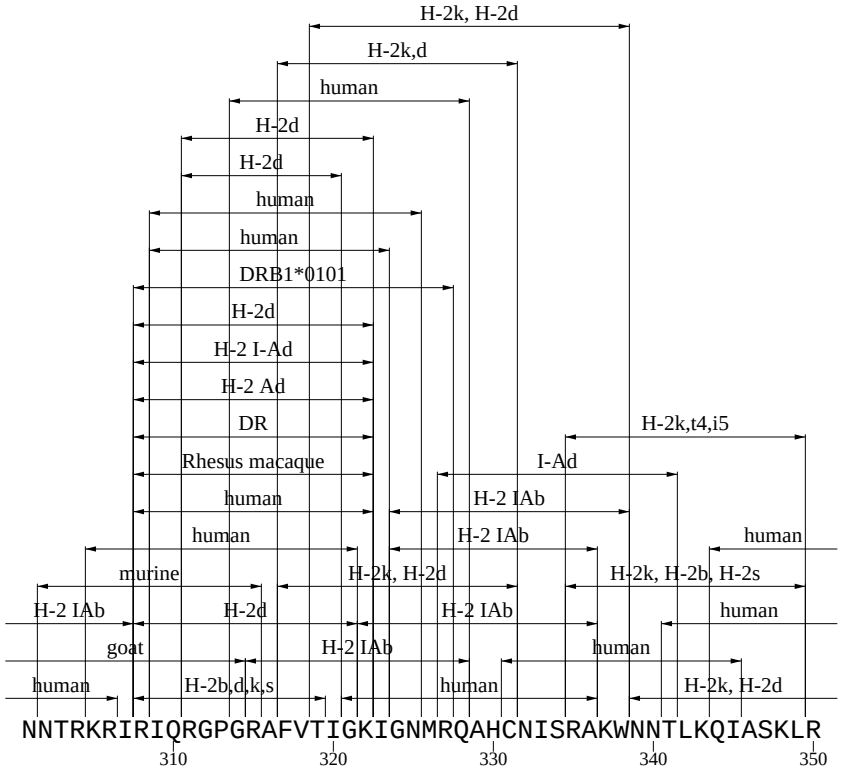

Rhesus macaque
human
human
human
H-2k,s
H-2k
Rhesus macaque
human
H-2k, H-2s
H-2d,i5
H-2d, H-2b
human
HLA-DR
human
H-2bxk
human
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIME
110
120
130
140
150

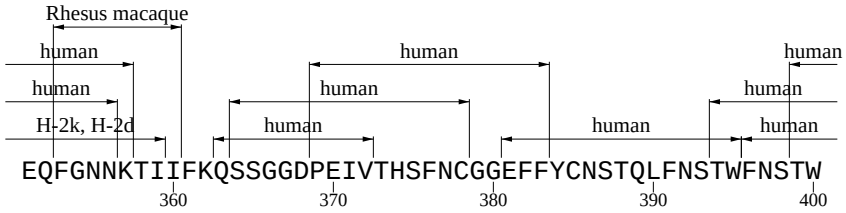

H-2bxk
H-2 IAb
H-2 IAb
H-2 IAb
H-2d
H-2 IAb
DR2
HLA-DR
unknown
H-2bxk,sxd
H-2 IAb
human, chimpanzee
H-2 IAb
human
Rhesus macaque
human
DRB1*0406
H-2 IAb
H-2 IAb
DR2,6
human
H-2k
H-2 IAb
human
Rhesus macaque
human
ITQACPKVSFEPIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHG
210
220
230
240
250

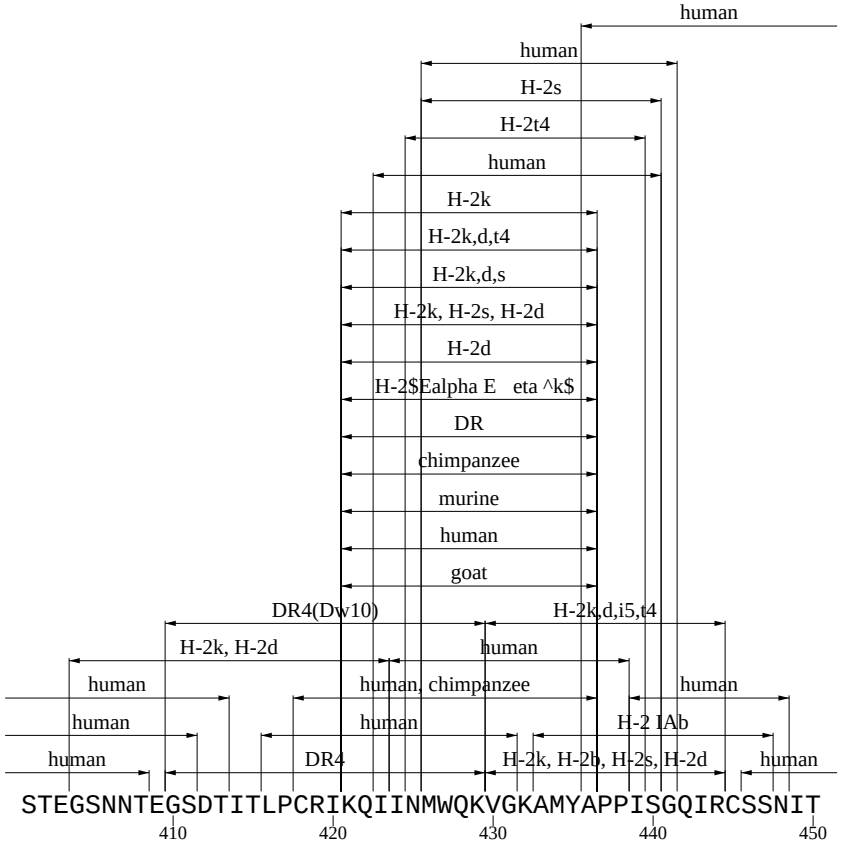

human
Rhesus macaque
H-2k
HLA-DR
H-2 IAb
Rhesus macaque
H-2 IAb
H-2 IAb
KGEIKNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSV
160
170
180
190
200

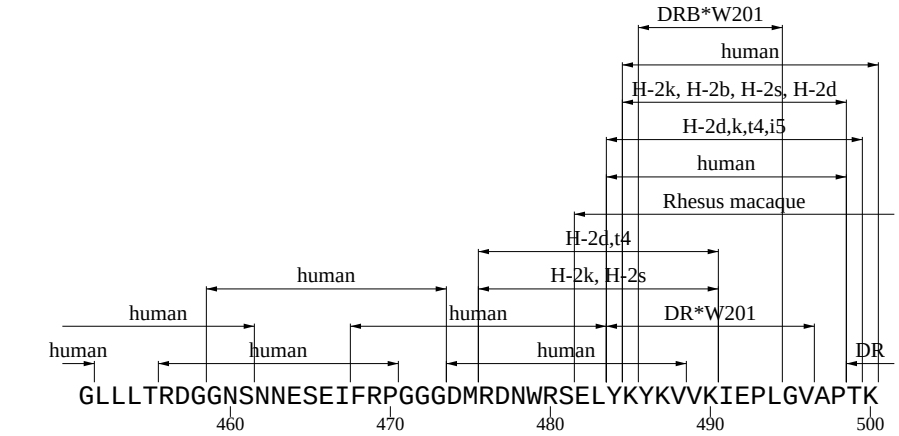

human
human
human
goat
HLA-DR
DRB1*0406
human
human
H-2bxk,sxd
human
human
human
H-2 IAb
human, chimpanzee
IRPVVSTQLLLNGSLAEEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPN
260
270
280
290
300

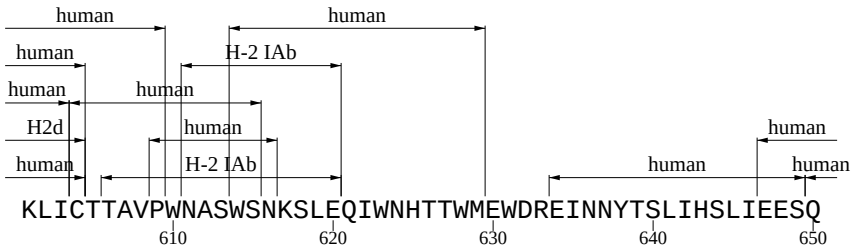
Helper T


H-2k, H-2d
H-2k,d
human
H-2d
H-2d
human
human
DRB1*0101
H-2d
H-2 I-Ad
H-2 Ad
DR
H-2k,t4,i5
Rhesus macaque
I-Ad
human
H-2 IAb
human
H-2 IAb
human
murine
H-2k, H-2d
H-2k, H-2b, H-2s
H-2 IAb
H-2d
H-2 IAb
human
goat
H-2 IAb
human
human
H-2b,d,k,s
human
H-2k, H-2d
NNTRKRIRIQRGPGRAFVTIGKIGNMRQAHCNISRAKWNNTLKQIASKLR
310
320
330
340
350

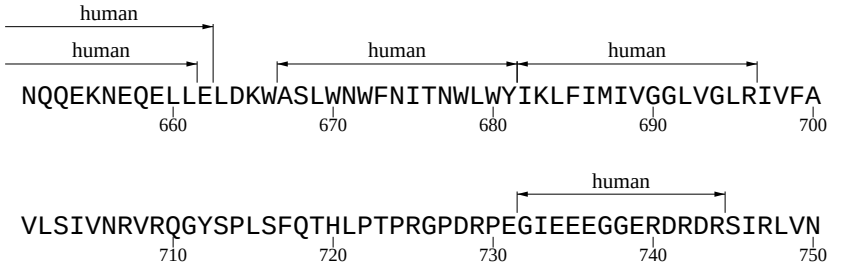

Rhesus macaque
human
human
human
human
human
H-2k, H-2d
human
human
human
EQFGNNKTIIFKQSSGGDPEIVTHSFNCGGEFFYCNSTQLFNSTWFNSTW
360
370
380
390
400


human
human
H-2s
H-2t4
human
H-2k
H-2k,d,t4
H-2k,d,s
H-2k, H-2s, H-2d
H-2d
H-2$Ealpha E eta ^k$
DR
chimpanzee
murine
human
goat
DR4(Dw10)
H-2k,d,i5,t4
H-2k, H-2d
human
human
human, chimpanzee
human
human
human
H-2 IAb
human
DR4
H-2k, H-2b, H-2s, H-2d
human
STEGSNNTEGSDTITLPCRIKQIINMWQKVGKAMYAPPISGQIRCSSNIT
410
420
430
440
450

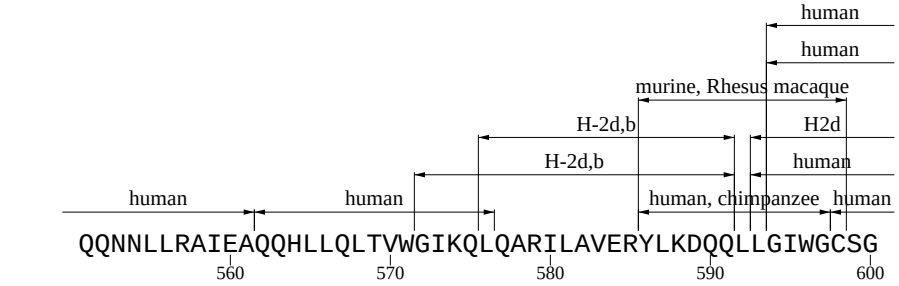

DRB*W201
human
H-2k, H-2b, H-2s, H-2d
H-2d,k,t4,i5
human
Rhesus macaque
H-2d,t4
human
H-2k, H-2s
human
human
DR*W201
human
human
human
DR
GLLLTRDGGNSNNESEIFRPGGGDMRDNWRSELYKYKVVKIEPLGVAPTK
460
470
480
490
500

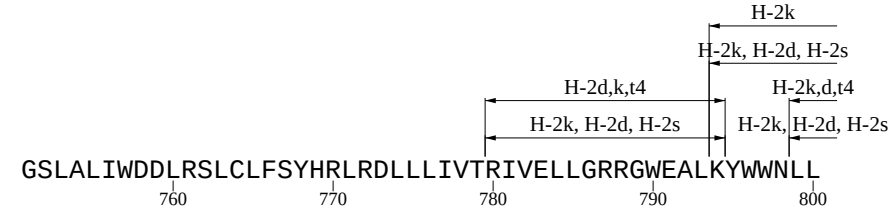

human
human
human
H-2 IAb
human
human
H2d
human
human
H-2 IAb
human
human
human
KLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHSLIEESQ
610
620
630
640
650


DR
Rhesus macaque
human
AKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQ
510
520
530
540
550


human
human
human
human
human
NQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRIVFA
660
670
680
690
700

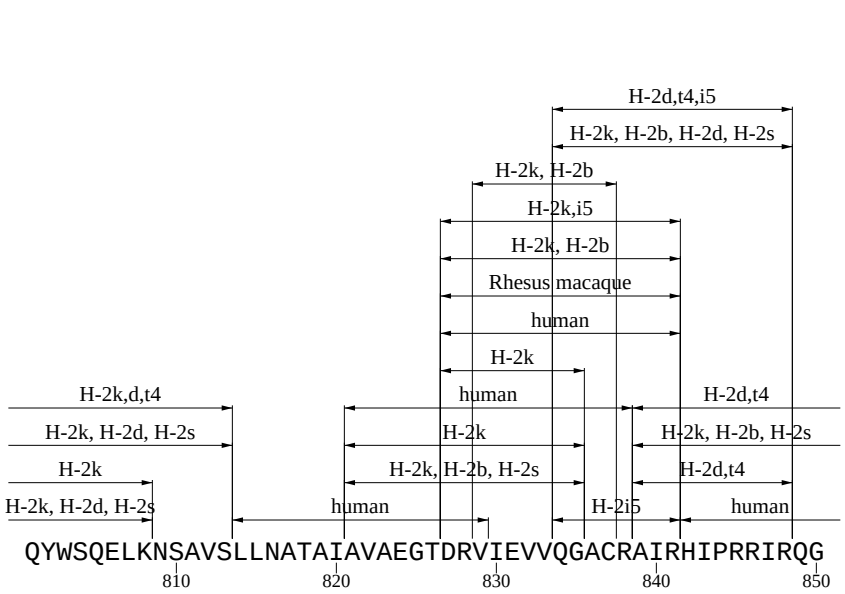
human
VLSIVNRVRQGYSPLSFQTHLPTPRGPDRPEGIEEEGGERDRDRSIRLVN
710
720
730
740
750

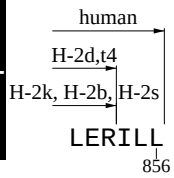

human
human
murine, Rhesus macaque
H-2d,b
H2d
H-2d,b
human
human
human
human, chimpanzee
human
QQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIWGCSG
560
570
580
590
600

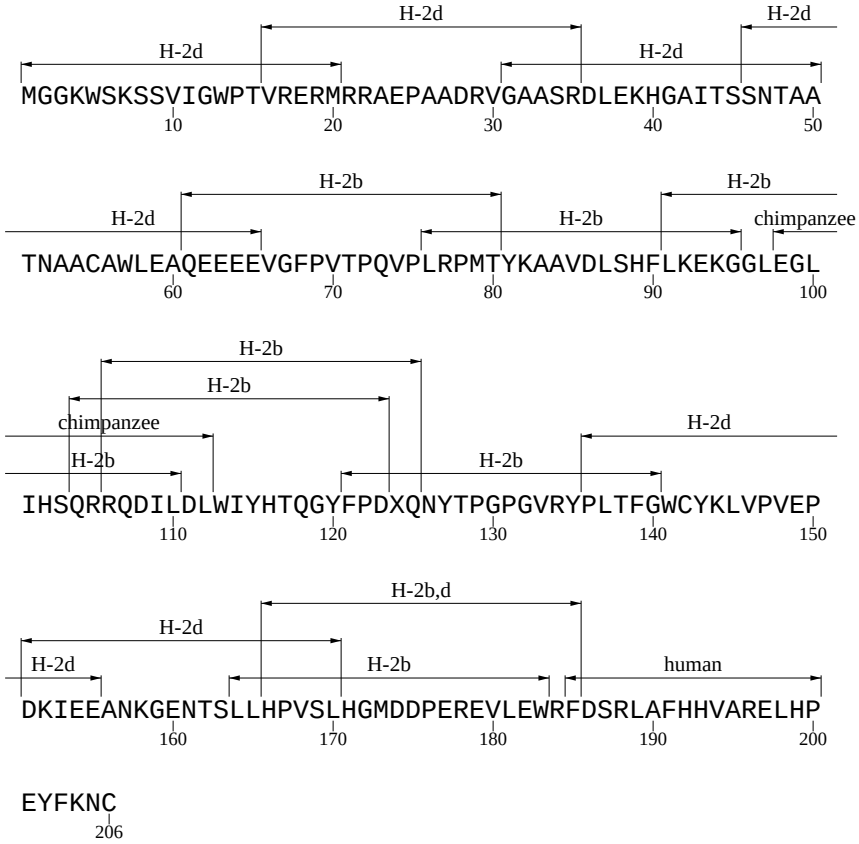

H-2k
H-2k, H-2d, H-2s
H-2d,k,t4
H-2k,d,t4
H-2k, H-2d, H-2s
H-2k, H-2d, H-2s
GSLALIWDDLRSLCLFSYHRLRDLLLIVTRIVELLGRRGWEALKYWWNLL
760
770
780
790
800

Helper T

Nef Helper Map







Part III-C: Helper T Cell References

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[Bedford (1997)] P. Bedford, L. B. Clarke, G. Hastings, & S. Knight. Primary Proliferative Responses to Peptides of HIV Gag p24. *J AIDS Hum Retrovirology* **14**:301–306, 1997. (Medline: 97265565) Notes: 23 overlapping 15-mer peptides from Gag p24 were used to pulse dendritic cells to identify epitopes by stimulating primary proliferative responses it *in vitro* from PBMC from healthy HIV-negative donors. Novel responses were detected.

[Bell (1992)] S. J. D. Bell, D. A. Cooper, B. E. Kemp, R. R. Doherty, & R. Penny. Definition of an immunodominant T-cell epitope contained in the envelope gp41 sequence of HIV-1. *Clin Exp Immunol* **87**:37–45, 1992. (Medline: 92127899) Notes: This gp41 peptide consistently elicits both T-cell blastogenic and B-cell (antibody) responses in asymptomatic HIV-seropositive individuals but not in ARC and AIDS patients. gp41 epitope: LGIWGCSGKLIC.

[Berzofsky (1988)] J. A. Berzofsky, A. Bensussan, K. B. Cease, J. F. Bourge, R. Cheynier, Z. Lurhama, J.-J. Salaun, R. C. Gallo, G. M. Shearer, & D. Zagury. Antigenic peptides recognized by T lymphocytes from AIDS viral envelope-immune humans. *Nature* **334**:706–708, 1988. (Medline: 88318926) Notes: Test of response to synthetic peptides of lymphocytes from 14 healthy human volunteers who had been immunized with a rec vaccinia virus containing HIV gp160, then boosted with a recombinant fragment containing the carboxyl-terminal 40% of gp120. 8/14 showed a proliferative response to T1; 4/14 to T2. A reduced response to T2 in terms of both magnitude and frequency may have been because of the boost containing the region covering T1, but not T2, and because of the timing of sampling relative to immunization. Some HLA typing was done but no conclusive MHC restriction patterns were determined. Env epitopes: T1: KQIINMWQEVGLAMYA and T2: HEDIISLWDQSLK.

[Birk (1998)] M. Birk, J. I. Flock, A. Sonnerborg, & M. Sallberg. Coexisting members of HIV-1 p17 gene quasispecies represent proteins with distinct antigenicity and immunogenicity. *AIDS* **12**:1973–81, 1998. (Medline: 99030030).

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(Medline: 92013142) Notes: 20% of T-cell clones from individuals innoculated with a recombinant nonglycosylated form of gp120 failed to respond to glycosylated protein. The epitope for one such clone was mapped and contained two glycosylated asparagines. Thus N-linked carbohydrates can abrogate antigen recognition by T lymphocytes.

[Boyer (1999)] J. D. Boyer, M. A. Chattergoon, K. E. Ugen, A. Shah, M. Bennett, A. Cohen, S. Nyl and , K. E. Lacy, M. L. Bagarazzi, T. J. Higgins, Y. Baine, R. B. Ciccarelli, R. S. Ginsberg, R. R. MacGregor, & D. B. Weiner. Enhancement of cellular immune response in HIV-1 seropositive individuals: A DNA-based trial. *Clin Immunol* **90**:100–7, 1999. (Medline: 99102724).

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[Calarota (1999)] S. A. Calarota, A. C. Leandersson, G. Bratt, J. Hinkula, D. M. Klinman, K. J. Weinhold, E. Sandstrom, & B. Wahren. Immune responses in asymptomatic HIV-1-infected patients after HIV-DNA immunization followed by highly active antiretroviral treatment.. *J Immunol* **163**:2330–8, 1999. (Medline: 99370046).

[Callahan (1990)] K. M. Callahan, M. M. Fort, E. A. Obah, E. L. Reinherz, & R. F. Siliciano. Genetic variability in HIV-1 gp120 affects interactions with HLA molecules and T-cell receptor. *J Immunol* **144**:3341–3346, 1990. (Medline: 90229719) Notes: Synthetic peptides representing a defined CD4+ human T-cell epitope in gp120 were used to survey gp120 molecules from various HIV-1 strains for the capacity to be recognized in the context of a single human MHC molecule, DR4. gp120 epitope: GSDTITLPCRIKQFINMWQE.

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this study presents evidence that 18 envelope and 12 gag peptides could stimulate T-cell proliferative responses from multiple representatives among 99 HIV infected study subjects. Thirty-six seronegative subjects were used as controls.

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