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could bind, which suggested that quantitative difference in binding constants may ultimately determine in vivo MHC restriction.


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15 of the peptides including T cell epitopes, gave significant binding.


[Callan (1998)] M. F. C. Callan, L. Tan, N. Annels, G. S. Ogg, J. D. K. Wilson, C. A. O’Callghan, N. Steven, A. J. McMichael, & A. B. Rickinson. Direct Visualization of Antigen-specific CD8+ T Cells during the Primary Immune Response to Epstein-Barr Virus in vivo. *J Exp Med* **187**:1395–1402, 1998. (Medline: 92387221) Notes: CTL effectors that killed HLA-matched HIV-1-infected H9 target cells or doubly transfected P815-A2-env, gag or nef mouse tumor cells, which expressed the viral antigens in association with HLA-A1/A3 or HLA-A2, were isolated in children born to HIV-1-infected mothers. HIV-1-specific CTL were detected less than 2 months after birth, and declined with disease progression. CTL were detected in the PBMC of three children who subsequently became seronegative.

[Cheynier (1992)] R. Cheynier, P. Langlade-Demoyen, S. B. S., G. Blondin, S. Wain-Hobson, C. Griscelli, E. Vilmer, & F. Plata. Cytotoxic T lymphocyte responses in the peripheral blood of children born to human immunodeficiency virus-1-infected mothers. *Eur J Immunol* **22**:2211–2217, 1992. (Medline: 98001384) Notes: Peptide competition experiments for presentation of viral peptides restricted by HLA-A3 and HLA-B27 was performed to study the specificity of peptide binding to class I molecules. HIV-1 Nef (74-82) presentation by HLA-A3 was among the epitopes studied.

[Carreno (1992)] B. M. Carreno, S. Koenig, & J. E. C. W. E. Biddison. The peptide binding specificity of HLA class I molecules is largely allele-specific and non-overlapping. *Molecular Immunol* **29**:1131–1140, 1992. (Medline: 92357052) Notes: Peptide competition experiments for presentation of viral peptides restricted by HLA-A3 and HLA-B27 was performed to study the specificity of peptide binding to class I molecules. HIV-1 Nef (74-82) presentation by HLA-A3 was among the epitopes studied.

[Casement (1995)] K. S. Casement, P. N. Nehete, R. B. Arlinghaus, & K. J. Sastry. Cross-reactive cytotoxic T lymphocytes induced by V3 loop synthetic peptides from different strains of human immunodeficiency virus type 1. *Virology* **211**:261–267, 1995. (Medline: 95373144) Notes: Seven diverse V3 peptides were found to induce CTL in immunized mice. All contained the H-2D\(^d\) binding motif G, P and R at positions 2, 3 and 5. Only a CTL, (no antibody response), was detected in immunized mice.


[Chen (1990)] B. Chen, J. Rothbard, & P. Parham. Apparent lack of MHC restriction in binding of class I HLA molecules to solid phase peptides. *J Exp Med* **172**:931–936, 1990. (Medline: 90354794) Notes: 64 viral antigenic peptides HLA-A,B,C heavy chains, and clathrin light chains were tested for binding to HLA-A2.1, Aw68.1, Aw69, B44, and B5. 15 of the peptides including T cell epitopes, gave significant binding.

[Cheynier (1992)] R. Cheynier, P. Langlade-Demoyen, M. R. Marescot, S. B. S., G. Blondin, S. Wain-Hobson, C. Griscelli, E. Vilmer, & F. Plata. Cytotoxic T lymphocyte responses in the peripheral blood of children born to human immunodeficiency virus-1-infected mothers. *Eur J Immunol* **22**:2211–2217, 1992. (Medline: 92387221) Notes: CTL effectors that killed HLA-matched HIV-1-infected H9 target cells or doubly transfected P815-A2-env, gag or nef mouse tumor cells, which expressed the viral antigens in association with HLA-A1/A3 or HLA-A2, were isolated in children born to HIV-1-infected mothers. HIV-1-specific CTL were detected less than 2 months after birth, and declined with disease progression. CTL were detected in the PBMC of three children who subsequently became seronegative.

Notes: Peptides from influenza and HIV-1 tested for their ability to promote the assembly of HLA-A2 and HLA-B51 molecules in T2 cell lysates. HIV Pol 476-484 allowed significant assembly of HLA-A2, and is a target for CTL. Nef peptide 186-194 produced significant assembly of HLA-B51. A hydrophobic anchor residue (V, L, I) at position 9 could occupy pocket F, and a hydrophobic residue (V, L) at position 3 or 4 may anchor to hydrophobic pocket D of HLA-B51. Proline at position 2 increases HLA-B51 anchoring.


Notes: Viral sequences across this region were compared from 3 HLA-A11 positive and 10 negative donors. Substitutions that were found only in the 3 HLA-A11 donors did not promote HLA-A11 assembly. Substitutions that were found in both HLA-A11 positive and negative donors, however, did not markedly alter the reactivity of the peptides. This suggests that substitutions that result in loss of HLA-A11 occur mainly in HLA-A11 positive donors.


Notes: Nef specific CTL were generated from six seropositive donors. Six epitopes were defined, all localized to two regions in the central part of Nef. Some epitopes could be recognized in the contexts of several HLA class I molecules. Peptides were based on BRU epitopes: QVPLRPMTYK, HLA A3, A11, B35: AAVDL-SHFLKEK, HLA A11; HTQGYFPQWQ, HLA B17;TQGYFPQWQNT, HLA B17, B37; NYTPGPGVRYPLT, HLA B7; and GVRYPLFTGWCYK-LVP, HLA B18.


Notes: Using synthetic peptides, six conserved epitopes on gp120 Env were identified, recognized by polyclonal human CTL in association with HLA-A2 class I. Conserved epitopes: RIQRGP-GRAFVTIGK, IIB; LWVTVYYGVPWKEATTTLFC; TTSYLTLCSNTSVITQACP; SVEINCTPRNNNRKSL; PEIVTHS; KCNGEFEY-CNS; LPRIKQF1NMWQEVGKAMY; VKIEPLVAPTKAKRRVQVR. control: gag, YKRWIIILNKIVRMYSPT, HLA B27.


[Goulder (1997b)] P. Goulder, A. Sewell, D. Laloo, D. Price, J. Whelan, J. Evans, G. Taylor, G. Luzzi, P. Giangrande, R. Phillips, & A. J. McMichael. Patterns of immunodominance in HIV-1-specific cytotoxic T lymphocyte responses in two human histocompatibility leukocyte antigens (HLA)-identical siblings with HLA-A*0201 are influenced by epitope mutation. *J Exp Med* **182:**1423–33, 1997b. (Medline: 97272078) Notes: Primary human immunodeficiency virus (HIV) infection is controlled principally by HIV-specific cytotoxic T lymphocytes (CTL) to a steady-state level of virus load, which strongly influences the ultimate rate of progression to disease. Epitope selection by CTL may be an important determinant of the degree of immune control over the virus. This report describes the CTL responses of two HLA-identical hemophiliaic brothers who were exposed to identical batches of Factor VIII and became seropositive within 10 wk of one another. Both have HLA-A*0201. The CTL responses of the two siblings were very dissimilar, one donor making strong responses to two epitopes within p17 Gag (HLA-A*0201-restricted SLYNTVATL and HLA-A3-restricted RLRPGGKKK). The sibling responded to neither epitope, but made strong responses to two epitopes presented by HLA-B7. This was not the result of differences in presentation of the epitopes. However, mutations in both immunodominant epitopes of the p17 Gag responder were seen in proviral sequences of the non-responder. We then documented the CTL responses to two HLA-A*0201-restricted epitopes, in Gag (SLYNTVATL) and Pol (ILKEPVHG) in 22 other HIV-infected donors with HLA-A*0201. The majority (71)responses to the Gag epitope. In the 29Gag epitope in standard assays, there was evidence of low frequency memory CTL responses using peptide stimulation of PBMC, and most of these donors also showed mutations in or around the Gag epitope.


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97047818).

[Haas (1998)] G. Haas, A. Samri, E. Gomard, A. Hosmalin, J. Duntze, J. M.

[Hadida (1995)] F. Hadida, G. Haas, G. Zimmermann, A. Hosmalin, R. Spohn,
A. Samri, G. Jung, P. Debre, & B. Autran. CTLs from lymphoid organs rec-
ognize an optimal HLA-A2 restricted and HLA-B52 restricted nonapeptide and several epitopes in the C-terminal region of HIV-1 Nef.
CTL dilution analysis showed CTL recognition in the context of HLA B52 and A2.1, A2.2 and A2.4 in nanomolar concentrations. Molecular modeling sug-
gests motifs important for peptide binding to the pocket of an HLA-A2.1 molecule.

[Hadida (1992)] F. Hadida, A. Parrot, M. P. Kieny, B. Sadat-Sowti, C. Mayaud,
& P. Debre. Carboxyl-terminal and central regions of human immuno-
deficiency virus-1 NEF recognized by cytotoxic T lymphocytes from lymphoid 
**1691**–1698, 1996b. (Medline: 97118362) Notes: HIV-1 specific CTL can be detected in lymph 
nodes and spleens. The carboxyl-terminal domain of NEF is recognized by CTL in association with HLA-A1 and B8, with clonal frequencies of one 
CTL per $10^6$ splenic lymphocytes. The defined anchor residues of HLA*5801 can 
be used to predict epitopes in HIV-1 proteins, the CTL from HLA-B*57 pos- 
itive individuals have limited cross-presentation capacity with HLA*5801 targets. In this paper five new HLA-B*57 epitopes were defined.

[Gray (1999)] C. M. Gray, J. Lawrence, J. M. Schapiro, J. D. Atman, M. A.
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Immunodeficiency Virus gag particles as an antigen carrier system: induction 
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[Haas (1998)] G. Haas, A. Samri, E. Gomard, A. Hosmalin, J. Duntze, J. M.
antigen-specific CTL response compared to that with VC1-F alone. VC1-F plus IL-12 expression plasmid or VC1-F alone were inoculated to BALB/c mice twice at interval of 2 weeks. Two weeks after the second inoculation, spleen effector cells from these mice were examined. Stronger CTL responses against target cells were observed from the inoculation of VC1-F plus IL-12 plasmid than from that with VC-1F alone, but there was no difference in antibody induction. The inoculation of VC1 plus IL-12 plasmid also produced higher CTL activity than the inoculation of VC1 alone. These augmented CTL activities were not observed using target cells pulsed with non-HIV-specific peptides and different class I haplotype cells. These data demonstrate that co-inoculation of cell-mediated immune potent antigen and IL-12 plasmids can enhance the antigen-specific CTL response. This may be a potential approach for the induction of cellular immunization against HIV-1 and other diseases.


Notes: Two peptide processing pathways are utilized for MHC class I presentation of HIV-1 Env epitopes. The previously characterized TAP-1 and TAP-2 dependent pathway can generate all Env epitopes and uses Env protein mislocalized in the cytosol to produce peptides. The second, novel pathway uses a TAP-1 independent pathway, and allows a subset of MHC restricted epitopes to be processed in the endoplasmic reticulum or a Golgi compartment.


Notes: A HLA DPw4.2 human CTL epitope located in gp41 was described, recognized by CD4+ CTL clones that were induced in seronegative humans by immunization with recombinant gp160 BRU. gp41 CTL epitope: GIKQLQARILA VERYLKDQ.


Notes: The amino acid stretch YMDD is a critical functional domain of reverse transcriptase, and is highly conserved. This sequence is also part of an HLA-A2-restricted epitope. The substitution YMDD to YVDD confers drug resistance to FTC and dideoxyinosine, and also abolishes the CTL specific response.


[Hickling (1990)] J. K. Hickling, C. M. Fenton, K. Howl and , S. G. Marsh, & J. B. Rothbard. Peptides recognized by class I restricted T-cells also bind to MHC class II molecules. *International Immunology* 2:435–441, 1990. (Medline: 91197875) Notes: Peptides shown to be presented in the context of MHC class I proteins by mouse or human CD8+ T lymphocytes could also bind to HLA-DR molecules on the surface of B lymphoblastoid cell lines (B-LCL). Four out of five class I restricted T cell determinants bound, including the HIV-1 gp120 epitope.

[Hill (1992)] A. V. Hill, J. Elvin, A. C. Willis, M. Aidoo, C. E. Allsopp, F. M. Gotch, X. M. Gao, M. Takiguchi, B. M. Greenwood, & A. R. Townsend et al. Molecular analysis of the association of HLA-B53 and resistance to severe malaria (see comments). *Nature* 360:434–9, 1992. (Medline: 93078872) Notes: The protective association between the human leukocyte antigen HLA-B53 and severe malaria was investigated by sequencing of peptides eluted from this molecule followed by screening of candidate epitopes from pre-erythrocytic-stage antigens of Plasmodium falciparum in biochemical and cellular assays. Among malaria-immune Africans, HLA-B53-restricted cytotoxic T lymphocytes recognized a conserved nonamer peptide from liver-stage-specific antigen-1 (LSA-1), but no HLA-B53-restricted epitopes were identified in other antigens. These findings indicate a possible molecular basis for this HLA-disease association and support the candidacy of liver-stage-specific antigen-1 as a malaria vaccine component.


[Jardetzky (1991)] T. S. Jardetzky, W. S. Lane, R. A. Robinson, D. Monteori, & D. C. Wiley. Identification of self peptides bound to purified HLA-B27. *Nature* 353:326–9, 1991. (Medline: 93078872) Notes: The protective association between the human leukocyte antigen HLA-B53 and resistance to severe malaria was investigated by sequencing of peptides eluted from this molecule followed by screening of candidate epitopes from pre-erythrocytic-stage antigens of Plasmodium falciparum in biochemical and cellular assays. Among malaria-immune Africans, HLA-B53-restricted cytotoxic T lymphocytes recognized a conserved nonamer peptide from liver-stage-specific antigen-1 (LSA-1), but no HLA-B53-restricted epitopes were identified in other antigens. These findings indicate a possible molecular basis for this HLA-disease association and support the candidacy of liver-stage-specific antigen-1 as a malaria vaccine component.


[Jardetzky (1991)] T. S. Jardetzky, W. S. Lane, R. A. Robinson, D. Madden, & D. C. Wiley. Identification of self peptides bound to purified HLA-B27. *Nature* 353:326–9, 1991. (Medline: 92018188) Notes: A pool of endogenous peptides bound to the human class I MHC molecule, HLA-B27, has been isolated. Microsequence analysis of the pool and of 11 HPLC-purified peptides provides information on the binding specificity of the HLA-B27 molecule. The peptides all seem to be nonamers, seven of which match to protein sequences in a database search. These self peptides derive from abundant cytosolic or nuclear proteins, such as histone, ribosomal proteins, and members of the 90K heat-shock protein family.


alpha (TNF-α), and TNF-β upon contact with target cells presenting viral antigen was assessed. Epitopes: p17: KIRLRPGKKKYKLHIVWASRELE, A3; gp41: VERYLKDQQL, B14 and A28, ERYLKDQQL, B14; RT: AIFQSSMTKILEPFRKQNPDIVIQ, A11; and Nef SQRRQDILDLWIHTQGYFPDQNY, B13.


[Johnson (1994a)] R. P. Johnson, S. A. Hammond, A. Trocha, R. F. Siliciano, & B. D. Walker. Epitope specificity of MHC restricted cytotoxic T lymphocytes induced by candidate HIV-1 vaccine. *AIDS Research and Hum Retroviruses* 10, Supp 2:S73–S75, 1994a. (Medline: 95169519) Notes: Volunteers were immunized with recombinant vaccinia virus expressing HIV-1 gp160 (vac-env) and boosted with recombinant gp160 (rgp160). CTL clones were analyzed for HLA restriction and specificity. An immunodominant HLA-A3.1 restricted epitope was observed that showed very little sequence variation among B subtype sequences, (TVYYGVPVWK). Naturally occurring variants of this peptide were able to stimulate reactivity. Two additional CD8+ CTL epitopes from vaccinees were characterized, as well as two CD4+ CTL epitopes.

[Johnson (1994b)] R. P. Johnson, S. A. Hammond, A. Trocha, R. F. Siliciano, & B. D. Walker. Induction of a major histocompatibility complex class I-restricted cytotoxic T-lymphocyte response to a highly conserved region of human immunodeficiency virus type 1 gp120 in seronegative humans immunized with a candidate HIV-1 vaccine. *J Virol* 68:3145–3153, 1994b. (Medline: 94202302) Notes: In two volunteers, immunization with a single strain of HIV-1 induced CD4+ and CD8+ CTL that are specific for multiple conserved regions of HIV-1 and would be expected to recognize a broad range of viral isolates. The immunodominant gp120 epitope, gp120 TVYYGVPVWK, elicited CD8+ HLA-A3.1 restricted CTL, and this epitope is highly conserved. CTL specific for this epitope could lyse target cells sensitized with all known natural sequence variants. Additionally, CD8+ HLA-B35 and CD8+ HLA-B18 restricted epitopes were defined as well as two CD4+ cytotoxic T-cell gp120 epitopes: ITQACPKVSFEPIPHY-CAPAGFAI and NNTLKQDSTKLREQFG.


[Johnson (1991)] R. P. Johnson, A. Trocha, L. Yang, G. P. Mazzara, D. L. Panicalli, T. M. Buchanan, & B. D. Walker. HIV-1 gag-specific cytotoxic T lymphocytes recognize multiple highly conserved epitopes. Fine specificity of the gag-specific response defined by using unstimulated peripheral blood mononuclear cells and cloned effector cells. *J Immunol* 147:1512–1521, 1991. (Medline: 91349569) Notes: This study presented a detailed study of gag specific CTL from HIV-1 seropositive individuals. Seven p24 and two p17 epitopes were described, that were recognized by class I restricted CD3+CD8+ CTL. p17 epitopes: KIRLRPGKKKYKLHIVWASRELE and QT-GEELRLSYNTATLYCVHQRIE; p24 epitopes: NPPVPGEYIKRUILGLNKIV, VHQAISPSRTLNAWVKVVEEKAFL, NAWSKVVVEEKSPEVIPMFSALSEGATPDQLNTMLNTVGH, GHQAAMQMLKETINEEAEWDR, and RAEQASQEVK.


[Kalams (1994)] S. Kalams, R. P. Johnson, A. K. Trocha, M. J. Dynan, H. S. Ngo, R. T. D’Aquila, J. T. Kurnick, & B. D. Walker. Longitudinal analysis of T-cell receptor (TCR) gene usage by HIV-1 envelope-specific cytotoxic T-lymphocyte clones reveals a limited TCR repertoire. *J. Exp. Med.* 179:1261–1271, 1994. (Medline: 94194282) Notes: This paper presents an in-depth longitudinal study of T-cell receptor gene usage to a well-defined HLA B14 restricted gp41 epitope. Ten CTL clones were derived from a single individual over 31 months. T-cell receptor V-D-J sequencing was performed on PCR amplification products. All ten clones utilized Vα14 and Vβ4 genes; observed limited T-cell receptor diversity to an immunodominant epitope was suggested to facilitate immune escape. gp41 epitope: ERYLKDQQL. An HLA B14 restricted RT epitope from this individual used Vα21 and Vβ14, showing use of these genes was not a feature of all HLA B14 restricted clones from this individual. RT epitope: AYLALQDGSLEVNVTDSQYALGI.


[Kim (1997a)] J. J. Kim, V. Ayyavoo, M. L. Bagarazzi, M. A. Chattergoon, K. Dang, B. Wang, J. D. Boyer, & D. B. Weiner. In vivo engineering of a cellular immune response by coadministration of IL-12 expression vector with a DNA immunogen. *J Immunol* 158:816–26, 1997b. (Medline: 97400332) Notes: This paper presents an in-depth longitudinal study of T-cell receptor gene usage to a well-defined HLA B14 restricted gp41 epitope. Ten CTL clones were derived from a single individual over 31 months. T-cell receptor V-D-J sequencing was performed on PCR amplification products. All ten clones utilized Vα14 and Vβ4 genes; observed limited T-cell receptor diversity to an immunodominant epitope was suggested to facilitate immune escape. gp41 epitope: ERYLKDQQL. An HLA B14 restricted RT epitope from this individual used Vα21 and Vβ14, showing use of these genes was not a feature of all HLA B14 restricted clones from this individual. RT epitope: AYLALQDGSLEVNVTDSQYALGI.


[Klein (1997)] M. R. Klein, J. Veenstra, A. M. Holwerda, M. T. Roos, I. Gow, G. Patou, R. A. Coutinho, W. D. F., & F. Miedema. Gag-specific immune responses after immunization with p17/p24:Ty virus-like particles in HIV type 1-seropositive individuals. *AIDS Res Hum Retroviruses* **13**:393–9, 1997. (Medline: 97229917) Notes: Gag-specific immune responses and changes in HIV-1 RNA levels were evaluated in eight HIV-1-infected persons, in order to assess the immunotherapeutic potential HIV-1 p17/p24:Ty virus-like particles (p24-VLP). All treated subjects showed transient and dose-dependent proliferative responses to the Ty-VLP carrier (stimulation index (SI), 2.0-119.5). Three of four individuals who received either 500 or 1,000 micrograms of p24-VLP also showed proliferative responses to p17 or p24 (SI, 2.0-15.7). In 2 subjects who were treated with either 500 or 1,000 micrograms of p24-VLP, enhanced Gag-specific CTL precursor (CTLp) frequencies were observed after immunization (10- to 14-fold). Both subjects had low baseline Gag-specific CTL activity (< 25 CTLp/10(6) PBMCs). In the other participants studied no significant boosting of preexisting Gag-specific CTL responses was observed. Short-term elevation of HIV-1 RNA levels at weeks 2 and 4 was observed in two subjects treated with the highest dose of p24-VLP. However, HIV-1 RNA levels at week 24 did not significantly differ from those found in the placebo group. In conclusion, p24-VLP induced marginal Gag-specific immune responses in limited numbers of HIV-1-seropositive individuals, with some showing short-term elevation of HIV-1 viral load. Further studies are needed to establish potential clinical effects of these observations.


[Klenerman (1995)] P. Klenerman, U.-C. Meier, R. E. Phillips, & A. J. McMichael. The effects of natural altered peptide ligands on the whole blood cytotoxic T lymphocyte response to human immunodeficiency virus. *Eur J Immunol.** 25**:1927–1931, 1995. (Medline: 95347391) Notes: This paper explores naturally occurring altered peptide ligands and their ability to sustain CTL, serve as antagonists to CTL specific for other variants, and to allow cell killing. The authors propose that a CTL response may be sustained in vivo that fails to recognize viral variants as they arise, proposing a mechanism for T-cell original antigenic sin.

[Klenerman (1994)] P. Klenerman, S. Rowland-Jones, S. McAdam, J. Edwards, S. Daenke, D. Lalloo, B. Koppe, W. Rosenberg, D. Boyd, A. Edwards, P. Giangrande, R. E. Phillips, & A. J. McMichael. Cytotoxic T-cell activity antagonized by naturally occurring HIV-1 Gag variants. *Nature* **369**:403–407, 1994. (Medline: 94255016) Notes: This paper documents that naturally occurring peptide variants can serve as antagonists, that is they can inhibit normal lysis of cells presenting the original epitope. The variants studied could serve as antagonists when they were processed from recombinant vaccinia, replicated HIV, or when they were synthetic peptides. Both agonist and antagonist sequences were found in the study subjects from whom the CTL clones were derived.


[Leggatt (1997)] G. R. Leggatt, M. A. Alexander-Miller, A. Kumar, S. L. Hoffman, & J. A. Berzofsky. Cytotoxic T lymphocyte (CTL) adherence assay (CAA): a non-radioactive assay for murine CTL recognition of peptide-MHC class I complexes. *J Immunol Methods* 201:1–10, 1997. (Medline: 97184603) Notes: This paper describes a novel assay, the CTL adhesion assay (CAA), and uses an HIV epitope in a murine system as a model system. CAA is a rapid, simple screening method for identifying cytolytic epitopes for a given CTL line, and may also identify peptides that cause T cell activation and adherence but not cytolysis. Cytotoxic T lymphocytes (CTL) form an important immune surveillance system against intracellular pathogens. Here we describe a simple, visual assay for identifying peptides specifically recognized by CTL, based on the discovery that CTL develop increased adhesive properties upon TCR triggering. Several CTL lines were shown to pellet to the bottom of a round bottom 96-well plate in the absence of peptide. In contrast, these same CTL lines incubated with their cognate peptide, allowing them to present peptide to each other, adhered to the sides of the well and were readily distinguished by macroscopic visual examination of the plate after 4-5 h or overnight incubation. This CTL adherence assay (CAA) demonstrated peptide specificity and MHC restriction, and was titratable with peptide concentration. With this technique, a minimal-sized, malaria CTL epitope was correctly identified from a panel of overlapping nonamers, although the adherence pattern of two mono-substituted, variant peptides was less.


son 3rd. Recognition of a small number of diverse epitopes dominates the
cytotoxic T lymphocytes response to HIV type 1 in an infected individual. 

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HIV type 1-seropositive subjects. *AIDS Res Hum Retroviruses* **11**:257–271, 
1995. (Medline: 95260535) Notes: Potent HIV-specific CTL lines were 
developed through culture of non-specific stimulation of T cell lines with 
autologous antigen presenting cells preincubated with HIV-1 peptides.

[Lieberman (1997b)] J. Lieberman, P. R. Skolnik, G. R. P. 3rd, J. A. Fabry, 
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[Littaua (1991)] R. A. Littaua, M. B. A. Oldstone, A. Takeda, C. Debouck, 
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C-Restricted CD8+ Cytotoxic T-Lymphocyte Clone Recognizes a Highly 
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ciano, & R. C. Bollinger. Characterization of a polyclonal cytolytic T lymphocyte response to human immunodeficiency virus in persons without clin-

ical progression. *J Infect Dis* **6**:1360–7, 1997. (Medline: 97323979) Notes: Five individuals were studied who survived HIV infection in good health for 
over 5 years. A broad polyclonal response was found to multiple proteins.

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phocyte responses by HIV gag particles carrying multiple immunodominant 

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does not use T-cell clones to map epitopes, but rather T-cell lines from HIVinfected donors. 20 amino acid peptides were used of map the region of the 
reactive epitopes. HLA restriction was not tested for all epitopes.

[McAdam (1995)] S. McAdam, P. Klenerman, L. Tussey, S. Rowland-Jones, 
D. Lalloo, R. Phillips, A. Edwards, P. Giangrande, A. L. Brown, & F. Gotch. Immunogenic HIV variant peptides that bind to HLA-B8 can fail to stimu-
Mononuclear cells in cytobrush specimens from the cervical samples were stimulated with antigen. Eight women with CD4 positive counts $\geq 500$ cells/µl had HIV-1 specific CTL, but only 4/11 with counts $< 500$ cells/µl had HIV-1 specific CTL responses.

CTL References


[McMichael & Walker(1994)] A. J. McMichael & B. D. Walker. Cytotoxic T lymphocytes epitopes: implications for HIV vaccine. *AIDS* 85:S155–S173, 1994. Notes: Comprehensive review summarizing CTL epitopes that have known HLA type and are fine mapped to indicate epitope boundaries. Anchor residues are indicated when known for different HLA restricted epitopes. Includes a summary of the published literature, as well as much work that was in press or submitted for publication.


[Nieltfeld (1995)] W. Nieltfeld, M. Bauer, M. Fevrier, R. Maier, B. Holzwarth, R. Frank, B. Maier, Y. Riviere, & A. Meyerhans. Sequence constraints and recognition by CTL of an HLA-B27-restricted HIV-1 gag epitope. *J Immunol* 154:2188–2197, 1995. (Medline: 95173425) Notes: Single point mutations were introduced into this epitope in the viral strain LAI, and the ability comparable peptides to sensitize ... of anchor residue R 264 to (L or G), results in infectious virus, and corresponding peptide has reduced binding af... of G 267 to K or E abrogated infectivity, and the peptide bound to HLA-B27, but did not serve as a target; thus nonrecognition of peptides derived from quasispecies analysis of a small region might not really be associated with an escape mutant, but rather a non-viable mutant.


[Nixon (1990)] D. F. Nixon, S. Huet, J. Rothbard, M.-P. Kieny, M. Delchambre, C. Thiria, C. R. Rizza, F. M. Gotch, & A. J. McMichael. An HIV-1 and HIV-2 cross-reactive cytotoxic T-cell epitope. *AIDS* **4**:841–845, 1990. (Medline: 91069449) Notes: An HLA-B27 specific CTL clone from an HIV-1 infected individual that reacts with the Gag SF2 epitope KRWIILGLNKIVRMY also cross-reacts with the HIV-2 ROD analog KRWIQLGKQSVRMY. The CTL also reacts with HIV-1 ELI KRWIVGLKIVRMY and SIVm142 RRWQQLGKQSRMY, but only at very high concentration of peptide with SIVk6w78 RRWQQLRKLQSRMY. The binding of the SIVk6w78 peptide to HLA-B27 does not seem to be reduced, so the authors suggest that the reduced ability to stimulate is in this case due to T-cell receptor interaction.


[Parker (1994)] K. C. Parker, M. A. Bednarek, & J. E. Coligan. Scheme for ranking potential HLA-A2 binding peptides based on independent binding of individual peptide side-chains. *J Immunol* **152**, 1994. (Medline: 94075819) Notes: The authors conclude that peptide amino acid side-chain binding to the HLA-A2 molecule is independent of the sequence of the peptide, and
developed a table of coefficients that can be used to help predict peptide binding to HLA-A2.


[Porgador (1997)] A. Porgador, H. F. Staats, B. Faiola, E. Gilboa, & T. J. Palker. Intranasal immunization with CTL epitope peptides from HIV-1 or ovalbumin and the mucosal adjuvant cholera toxin induces peptide-specific CTLs and protection against tumor development in vivo. *J Immunol* **158**:834–41, 1997. (Medline: 97146054) Notes: To evaluate the ability of mucosal immunization protocols using peptide immunogens to induce CTL responses, BALB/c and C57BL/6 mice were immunized intranasally (i.n.) with peptides corresponding to a known CTL epitope in HIV-1 glycoprotein 120 or OVA, respectively, and the mucosal adjuvant cholera toxin (CT). Intranasal immunization of BALB/c mice with a 10- or 15-amino acid peptide corresponding to a CTL determinant in HIV-1 glycoprotein 120 and CT induced peptide-specific CTLs in spleen cells that persisted through 35 days after the last immunization. Intranasal immunization of C57BL/6 mice with the octameric OVA peptide and CT produced similar results with detectable peptide-specific CTL in both the cervical lymph node and spleen. To test whether CTL induced by i.n. immunization with OVA peptide and CT were functional in vivo, groups of C57BL/6 mice were injected with E.G7- OVA tumor cells that express the OVA protein and monitored for tumor growth. Animals immunized i.n. with OVA and CT were protected against tumor development as efficiently as animals immunized by the potent CTL induction protocol of i.v. injection with OVA-pulsed dendritic cells. Intranasal immunization with peptides corresponding to known CTL epitopes and CT provides a noninvasive route of immunization for the induction of CTL responses in vivo.

release from stimulated CTL clones derived from either the peripheral blood or CSF of 3 patients was studied. HLA restriction was determined for two of seven clones. GM-CSF and TNF-α and IFN-γ were produced by all clones; most clones produced low amounts of IL-2, IL-3, and IL-4.


[Robertson (1993)] M. N. Robertson, F. Buseyne, O. Schwartz, & Y. Riviere. Efficient Antigen Presentation to Cytotoxic T Lymphocytes by cells transduced with a retroviral vector expressing the HIV-1 Nef Protein. *AIDS Res and Hum Retroviruses* 9:1217–1223, 1993. (Medline: 94190626) Notes: This paper presents a retroviral vector system for antigen presentation to CTLs. As part of the controls to test their system, they study the response to specific Nef peptides, which contain the dominant CTL epitopes in Nef in their study subject.


[Rowland-Jones (1998a)] S. Rowland-Jones, T. Dong, P. Krausa, J. Sutton, H. Newell, K. Ariyoshi, F. Gotch, S. Sabally, T. Corrah, J. Kimani, K. MacDonald, F. Plummer, J. Ndinya-Achola, H. Whittle, & A. McMichael. The role of cytotoxic T-cells in HIV infection. *Dev Biol Stand* 92:209–14, 1998a. (Medline: 98214896) Notes: In this paper CTL response to previously defined conserved epitopes was found in exposed but uninfected prostitutes in Nairobi. Subtypes A and D are circulating in this regions, and the reactive epitopes tended to be conserved. Similarly previous studies in the Gambia showed that exposed but uninfected prostitutes tended to have B35 presented CTL epitopes conserved between HIV-1 and HIV-2. It was suggested that what was special about B35 is simply that it presents epitopes found both HIV-1 and HIV-2.


[Rowland-Jones (1993a)] S. L. Rowland-Jones, D. F. Nixon, M. C. Aldhous, F. Gotch, K. Ariyoshi, N. Hallam, J. S. Kroll, K. Froebeil, & A. McMichael. HIV-specific cytotoxic T-cell activity in an HIV-exposed but uninfected infant. *Lancet* 341:860–861, 1993a. (Medline: 93218363) Notes: The factors necessary for protective immunity against HIV-1 are unknown. Important information about these factors should come from study of people at high risk of HIV infection who have not apparently become infected. Among these are the estimated 60-85who may be exposed in utero or perinatally to HIV-1 but do not become infected. We observed the transient appearance of HIV-specific cytotoxic T-lymphocyte (CTL) activity in a baby born to HIV-1-infected parents, in whom all standard markers of infection remained negative. These findings suggest that HIV-specific CTLs may be a marker for recently exposed, but uninfected, individuals.


[Safrit (1994a)] J. T. Safrit, C. A. Andrews, T. Zhu, D. D. Ho, & R. A. Koup. Characterization of human immunodeficiency virus type 1-specific cytotoxic T lymphocyte clones isolated during acute seroconversion: recognition of autologous virus sequences within a conserved immunodominant epitope. *J Exp Med* 179:463–472, 1994a. (Medline: 94125027) Notes: HIV-1 specific CTL clones were isolated from two individuals at acute seroconversion. In one patient, two HLA A31-restricted clones recognized the same fragment of gp41, peptide RLRLDLLVTR, but one was sensitive to a Thr to Val substitution, while the other was not. A CTL HLA A32-restricted clone from the other patient recognized the gp41 peptide VLSVNRVRQGYSPLSFQTH. Autologous viral sequences from seroconversion were recognized by the CTL clones, but not the HIV-1 strain MN.

[Safrit (1994b)] J. T. Safrit, A. Y. Lee, C. A. Andrews, & R. A. Koup. A region of the Third Variable Loop of HIV-1 gp120 is recognized by HLA-B7-Restricted CTLs from two acute seroconversion patients. *J Immunol* 153:3822–3830, 1994b. (Medline: 95015873) Notes: HIV-1 envelope-specific CTL clones were isolated from the peripheral blood of two patients within weeks of seroconversion. These clones were CD8+ and restricted by the HLA-B7 molecule. The minimum epitope was defined, RPNNTRKSI, with anchor residues at the proline and isoleucine; the anchor residues are relatively well conserved. A serine to arginine change at position 9 of the epitope abrogated clone recognition in one of the patients. This amino acid change is one factor that has been associated with a change from a nonsyncytium-inducing to a syncytium-inducing phenotype of HIV-1.


Shirai (1997)] M. Shirai, S. Kozlowski, D. H. Margulies, & J. A. Berzofsky. Degenerate MHC restriction reveals the contribution of class I MHC molecules in determining the fine specificity of CTL recognition of an immunodominant determinant of HIV-1 gp160 V3 loop. *J Immunol* **158**:3181–8, 1997. (Medline: 97240759) Notes: The novel allogegenic presentation of an immunodominant determinant within the HIV-1 gp160 V3 loop by three different class I MHC molecules to the same CD8+ CTL is used to study the influence of the MHC molecule on the fine specificity of CTL recognition. We previously reported that four distinct class I molecules of H-2d,u,p,q presented the V3 decacapptide P18-I10 (RGPGRAFVT1) to CTL. Surprisingly, we found that H-2d,u,p cells mutually cross-present the P18-I10 peptide to allogeneic CTL clones of each of the other haplotypes, whereas none of these cross-presents to H-2q CTL, nor do H-2q targets present to CTL of the other haplotypes. Here, we explore the critical amino acid residues for the cross-presentation using 10 variant peptides with single amino acid substitutions. The fine specificity examined using these mutant peptides presented by the same MHC class I molecule showed striking similarity among the CTL of each haplotype, expressing either V beta 8.1 or V beta 14. In contrast, the fine s.


Shirai (1992)] M. Shirai, C. D. Pendleton, & J. A. Berzofsky. Broad recognition of cytotoxic T cell epitopes from the HIV-1 envelope protein with multiple class I histocompatibility molecules. *J Immunol* **148**:1657–1667, 1992. (Medline: 92176620) Notes: This paper explored the possibility that defined epitopes from HIV-1 Env might be presented by multiple class I genes to CTLs using a murine system, isolating CTL from mice immunized with gp160 expressing recombinant vaccinia virus. The CTL epitope at the tip of the V3 loop (P18) was found to be presented by class I MHC molecules from four of ten haplotypes tested. Peptides that had previously been defined as helper T cell determinants (T1 in gp120, and HP53 (also called TH4.3)) were also able to stimulate CTL from mice with multiple haplotypes.


Siliciano (1988)] R. Siliciano, T. Lawton, C. Knall, R. Karr, P. Berman, T. Gregory, & E. Reinherz. Analysis of Host-Virus Interactions in AIDS with anti-gp120 T-Cell Clones: Effect of HIV Sequence Variation and a Mechanism for CD4+ Cell Depletion. *Cell* **54**:561–575, 1988. (Medline: 88295131) Notes: This article demonstrated that a class II HLA-DR4 restricted response can be stimulated by CD4 uptake of gp120, suggesting a mechanism for T-cell depletion in vivo. This peptide containing the epitope was also able to stimulate a class I restricted, CD8+ CTL response.

Sipsas (1997)] N. V. Sipsas, S. A. Kalams, A. Trocha, S. He, W. A. Blattner, B. D. Walker, & R. P. Johnson. Identification of type-specific cytotoxic T lymphocyte responses to homologous viral proteins in laboratory workers accidentally infected with HIV-1. *J Clin Invest* **99**:752–62, 1997. (Medline: 97197584) Notes: To examine a situation where the autologous strain and the reference reagents would be the same, the CTL response of three lab workers accidentally infected with HIV IIIB was studied. Both group specific and type specific epitopes were targets for CTL clones. One subject had a broadening of CTL response over time, using a broad range of restricting HLA class I alleles. Characterization of the cytotoxic T lymphocyte (CTL) response against HIV-1 has been limited by the use of target cells expressing viral proteins from laboratory isolates of HIV-1. This approach has favored identification of group-specific CTL responses and precluded assessment of the extent of type-specific CTL responses directed against HIV-1. Using cells expressing viral proteins from the HIV-1 IIIB strain, we performed a detailed characterization of HIV-1-specific CTL response in three laboratory workers.
accidentally infected with HIV-1 IIIB. Eight of the epitopes identified were group specific, lying in relatively conserved regions of Gag, reverse transcriptase, and envelope. Three type-specific epitopes were identified, two of them in highly variable regions of envelope. In longitudinal studies in one subject, seven different epitopes and five different restricting HLA class I alleles were identified, with a progressive increase in the number of CTL epitopes recognized by this subject over.

[Smith (1996)] K. J. Smith, S. W. Reid, D. I. Stuart, A. J. McMichael, E. Y. Jones, & J. I. Bell. An altered position of the alpha 2 helix of MHC class I is revealed by the crystal structure of HLA-B*3501. *Immunity* 4:203–213, 1996. (Medline: 96209671) Notes: The crystal structure of HLA-B*3501 complexed with Nef epitope VPLRPMTY was determined at 2 angstrom resolution, revealing details about binding such as the structural basis for the tyrosine specificity of the F pocket.


construct, stimulated with peptides: SITKPGGRVIYATGQ, RF; RIQRGP-GRAFVTIGK, IIB; and RIHIGPGRFYTTKN, MN.


[Takeshita (1995)] T. Takeshita, H. Takahashi, S. Kozlowski, J. D. Ahlers, C. D. Pendleton, R. L. Moore, Y. Nakagawa, K. Yokomuro, B. S. Fox, D. H. Margulies, & J. A. Berzofsky. Molecular Analysis of the same HIV peptide functionally binding to both a class I and a class II MHC molecule. *J Immunol* 154:1973–1986, 1995. (Medline: 95138543 Notes: Of RGPGRAFVTI, the upper case amino acids iGPgRaFvtI are critical for binding, consistent with H-2Dd motif XGPX(RKH)XXX(X)(LIF). Stimulation of the HLA class II I-A d required a longer peptide, IQRGPGRAFVTI or RIQRGPGRAFVTI, and riqrpgRaFvti were essential for binding to the Class II molecule.


[Tobery & Siliciano (1997)] T. W. Tobery & R. F. Siliciano. Targeting of HIV-1 antigens for rapid intracellular degradation enhances cytotoxic T lymphocyte (CTL) recognition and the induction of de novo CTL responses in vivo after immunization. *J Exp Med* 185:909–20, 1997. (Medline: 97217373 Notes: CD8+ cytotoxic T lymphocytes (CTLs) have the ability to recognize and eliminate virally infected cells before new virions are produced within that cell. Therefore, a rapid and vigorous CD8+ CTL response, induced by vaccination, can, in principle, prevent disseminated infection in vaccinated individuals who are exposed to the relevant virus. There has thus been interest in novel vaccine strategies that will enhance the induction of CD8+ CTLs. In this study, we have tested the hypothesis that targeting an antigen to undergo more efficient processing by the class I processing pathway will elicit a more vigorous CD8+ CTL response against that antigen. Targeting a type I transmembrane protein, the HIV-1 envelope (env) protein, for expression in the cytoplasm, rather than allowing its normal co-translational translocation into the endoplasmic reticulum, sensitized target cells expressing this mutant more rapidly for lysis by an env-specific CTL clone. Additionally, a greatly enhanced de novo env-specific.

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effective, suggesting surface density of peptides may influence efficiency of CTL killing.


[van Baalen (1993)] C. A. van Baalen, M. R. Klein, A. M. Geretti, R. I. P. M. Keet, F. Miedema, C. A. C. M. van Els, & A. D. M. E. Osterhaus. Selective in vitro expansion of HLA class I-restricted HIV-1 Gag-specific CD8+ T-cells: cytotoxic T-lymphocyte epitopes and precursor frequencies. AIDS 7:781–786, 1993. (Medline: 93371704) Notes: Gag specific epitopes and precursor frequencies were studied in seven individuals; for CTLs from one individual, fine mapping was done using peptides. PFA-fixed rVV-Gag-infected B-LCL cells were used as stimulator cells of bulk PBMC cultures to determine precursor frequencies and identify epitopes.


[van Baalen (1997)] C. A. van Baalen, M. R. Klein, A. M. Geretti, R. I. P. M. Keet, F. Miedema, & A. D. M. E. Osterhaus. Human immunodeficiency virus type 1 Rev- and Tat-specific cytotoxic T lymphocyte frequencies inversely correlated with rapid progression to AIDS. J Gen Virol 78:1913–1918, 1997. (Medline: 97410272) Notes: CTLp frequencies to Rev and Tat were inversely correlated with rapid progression to AIDS, but not Gag, RT or Nef. 3/7 long term non-progressors and 0/5 progressors were positive for HLA-B57, so it was again found to be associated with long term survival.


totoxic T cells and neutralizing antibodies induced in rhesus monkeys by virus-like particle HIV vaccines in the absence of protection from SHIV infection. *Virology* **245**:65–74, 1998b. (Medline: 98277073) Notes: A VLP is a non-infectious virus like particle self-assembled from HIV Pr55 gag. Macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains. Gag and Env specific CTL were stimulated in each case, and Ab response to Gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4. Despite the CTL and Ab response, immunized macaques were infected by interventional challenge with SHIV chimeric challenge stock. Not all immunized monkeys had a CTL response, probably due to the outbred nature of the animals and polymorphic MHC alleles. Two macaques had CTL to gag, and one macaque had CTL to the CD4 binding region, and one animal responded to gp120 pooled peptides; none had a response to the V3 peptide.


[Yang (1997a)] O. O. Yang, S. A. Kalams, A. Trocha, H. Cao, A. Luster, R. P. Johnson, & B. D. Walker. Suppression of human immunodeficiency virus type 1 replication by CD8+ cells: evidence for HLA class I-restricted triggering of cytolytic and noncytolytic mechanisms. *J Virol* **71**:3120–8, 1997a. (Medline: 97213986) Notes: Although CD8+ lymphocytes in human immunodeficiency virus type 1 (HIV-1)-infected individuals have been demonstrated to suppress viral replication, the mechanisms of inhibition have not been defined precisely. A large body of evidence indicates that these cells act via soluble inhibitory factors, but the potential role of HLA class I-restricted cytolysis has remained controversial. Here we demonstrate that HIV-1-specific cytotoxic T lymphocytes (CTL) mediate antiviral suppression by both cytolytic and noncytolytic mechanisms. The predominant mechanism requires direct contact of CTL with the infected cells, is HLA class I-restricted, and can achieve complete elimination of detectable virus in infected cell cultures. Inhibition occurs even at high multiplicities of infection or at ratios of CTL to CD4 cells as low as 1:1,000. The other mechanism is mediated by soluble inhibitory factors which are triggered in an antigen-specific and HLA-restricted fashion but then act without HLA restriction.


