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References


[Back et al.(1993)] N. K. T. Back, L. Smit, M. Schutten, P. L. Nara, M. Tersmette, & J. Goudsmit. Mutations in human immunodeficiency virus type 1 gp41 affect sensitivity to neutralization by gp120 antibodies. *J. Virol.* 67:6897–6902, 1993. OTE: MEDLINE: 94016886 Three closely related clones were derived from a neutralization resistant IIIB isolate that had been passaged in a chimpanzee. gp41 mutations were shown to profoundly alter the ability of V3 loop MAbs 5023 and 178.1 to neutralize. Critical substitutions in gp41 were 668 and 675, close to the immunogenic domain 662-668, or ELDKWAS. Less profound inhibition was observed for the anti-CD4 binding site MAb GP13.

[Bagley et al.(1994)] J. Bagley, P. J. Dillon, C. Rosen, J. Robinson, J. Sodroski, & W. A. Marasco. Structural characterization of broadly neutralizing human monoclonal antibodies against the CD4 binding site of HIV-1 gp120. *Mol. Immunol.* 31(15):1149–1160, 1994. OTE: MEDLINE: 95021325 This paper is a detailed study of the V-D-J heavy chain usage and V-J light chain usage for the three monoclonals that bind to the HIV-1 envelope CD4 binding site: F105, 15e and 21h. Different germline genes were used, and there was evidence for antigen-drive clonal selection of somatic mutations. Eight positions in the heavy chain and two in the light chain complementarity determining positions were identical in the three Mabs.

[Binley et al.(1996)] J. M. Binley, H. J. Ditzel, C. F. Barbas III, N. Sullivan, J. Sodroski, P. W. H. I. Parren, & D. R. Burton. Human antibody responses to HIV type 1 glycoprotein 41 cloned in phage display libraries suggest three major epitopes are recognized and give evidence for conserved antibody motifs in antigen binding. *AIDS Res. Hum. Retroviruses* 12:911–924, 1996. OTE: Medline: 96392164 A panel of anti-gp41 human Fab fragments were generated by panning phage display antibody libraries prepared from HIV-1 positive donors with rgp41. Fabs tended to be directed against three epitopes, designated clusters I-III. None were neutralizing. A common CDR3 motif was found in several of the heavy chain sequences.
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[Bristow et al.(1994)] R. G. W. Bristow, A. R. Douglas, J. J. Skehel, & R. S. Daniels. Analysis of murine antibody responses to baculovirus-expressed human immunodeficiency virus type 1 envelope glycoproteins. J. Gen. Virol. 75:2089–2095, 1994. OTE: MEDLINE: 94322004 BALB/c mice were immunized with baculovirus expressed gp160 or gp120, and 15 MAbs were generated. No MAbs generated in this study neutralized reference strains, using a tetrazolium-based cytotoxicity assay to test for neutralization. Ten of the Mabs were mapped by peptide ELISA, and seven reacted with the C1 region, one with V2, one with V4, and one with the C-terminal end.

[Broder et al.(1994)] C. Broder, P. Earl, D. Long, S. Abedon, B. Moss, & R. Dom. Antigenic implications of human immunodeficiency virus type 1 envelope quaternary structure: Oligomer-specific and -sensitive monoclonal antibodies. Proc. Natl. Acad. Sci. USA 91:11699–11703, 1994. OTE: MEDLINE: 95062336 35 anti-gp41 and 27 anti-gp120 murine MAbs generated by immunization with oligomeric HIV-1 IIIB envelope were studied. These MAbs tended to react with conformational epitopes. 21 of the anti-gp41 MAbs reacted preferentially with gp120 oligomer, while only 1 of the anti-gp120 MAbs reacted more strongly with the oligomer, and 14 of the anti-gp120 preferentially recognized monomeric env.


[Buchbinder et al.(1992)] D. Burton, C. Barbas, M. Persson, S. Koenig, R. M. Chanock, & R. A. Lerner. A large array of human monoclonal antibodies to type 1 human immunodeficiency virus from combinatorial libraries of asymptomatic seropositive individuals. Proc. Natl. Acad. Sci. USA 88:10134–10137, 1991. OTE: MEDLINE: 92052225 A panel of human monoclonal antibody Fab fragments was generated against the surface of the gp120 glycoprotein of HIV-1 by antigen selection from a random combinatorial library prepared from 5 ml of bone marrow from an asymptomatic individual who had been HIV-positive for 6 years. These Fab variable regions were sequenced and were found to be diverse. Binding constants were measured and the Fabs generally bound gp120 with high affinity. The methods used to obtain this panel could be used to obtain antibodies to test passive immunization as a therapy for AIDS.
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[Cook et al. (1994)] D. G. Cook, J. Fantini, S. L. Spitalnik, & F. Gonzalez-Scarano. Binding of human immunodeficiency virus type 1 HIV-1 gp120 to galactosylceramide (GalCer): relationship to the V3 loop. *Virology* **201**:206–214, 1994. OTE: MEDLINE: 94240806 Antibodies against GalCer can block infection of CD4-negative cells from the brain and colon that are susceptible to HIV infection. This paper explores the ability of a panel to MAbs to inhibit binding of gp120 to GalCer, and also of the binding of GalCer to inhibit MAb-gp120 interaction. MAbs to the V3 loop and GalCer showed mutual inhibition of binding to gp120, and anti-CD4 binding site MAbs showed reduced inhibition. N- and C-terminal MAbs didn’t influence GalCer binding.


[Devico et al. (1995)] A. L. Devico, R. Rahman, J. Welch, R. Crowley, P. Lusso, M. G. Sarnagadharan, & R. Pal. Monoclonal antibodies raised against covalently crosslinked complexes of human immunodeficiency virus type 1 gp120 and CD4 receptor identify a novel complex-dependent epitope on gp120. *Virology* **211**:583–588, 1995. OTE: MEDLINE: 95373192 To explore the immunogenicity of regions of gp120 that are exposed due to conformational changes in gp120 upon CD4 binding, CD4 was covalently linked to gp120 and this complex was used as an immunogen for BALB/c mice. Two MAbs were produced, both of which bind preferentially to the gp120-CD4 complex, and are conformational. Competition assays indicate these MAbs bind to epitopes that are recognized by sera from HIV-1 infected humans.


[Ditzel et al. (1995)] H. J. Ditzel, J. M. Binley, J. P. Moore, J. Sodroski, N. Sullivan, L. S. W. Sawyer, R. M. Hendry, W.-P. Yang, C. F. Barbas III, & D. R. Burton. Neutralizing recombinant human antibodies to a conformational V2- and CD4-binding site-sensitive epitope of HIV-1 gp120 isolated by using an epitope-masking procedure. *J. Immunol.* **154**:893–906, 1995. OTE: MEDLINE: 95114416 A panel of Fabs was obtained from a library prepared from the bone marrow of a long-term asymptomatic HIV-1 seropositive male donor. Four Fabs recognize the CD4BS. An additional four Fabs were retrieved after epitope masking gp120 with the CD4BS Fabs at the screening stage. 3/4 of these Fabs represent a V2 dependent conformational epitope.


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In this paper, three anti-HIV-1 gp41 specific MAbs were found to react with astrocytes: 98-6, 167-7 and 15G1. Reactive astrocytes in the hippocampus were most prominently involved, and the antibodies stained no other cell type in the brain, kidney or liver. All three mapped to a conformationally dependent epitope between aa 644-663.


[**Fudauin et al.(1996)**] M.-C. Gauduin, G. P. Allaway, P. J. Maddon, C. F. Barbas III, D. R. Burton, & R. A. Koup. Effective ex vivo neutralization of human immunodeficiency virus type 1 in plasma by recombinant immunoglobulin molecules. *J. Virol.* **70**:2586–2592, 1996. OTE: MEDLINE: ? Virus direct from plasma from six HIV-1 infected individuals was used for neutralization assay. MAb 19b could neutralize 2/6 plasma samples, while MAb IgG1b12 could neutralize 5/6 plasma samples. CD4-based molecules were also tested: CD4-IgG2 was effective in the ex vivo assay, but sCD4 was not. Thus, MAbs IgG1b12 and CD4-IgG2 have broad and potent in vitro and ex vivo neutralizing activities.


MAbs that showed high HIV-1 neutralization. The amount of p24 in the sera of patients decreased in five patients, but remained the same or increased in six of them. The level of viral RNA in the plasma of patients decreased in four, showed no changes in another four and increased in the other three. By themselves, the MAbs did not appear to be efficient enough to decrease the virus burden in a permanent form in late-stage HIV patients.


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AIDS Res. Hum. Retroviruses 11:1153–62, 1995. OTE: MEDLINE: 96157202 To investigate how HIV-1 escapes from recognition, a panel of V3 peptides based on sequences derived from 6 HIV-1 positive individuals was tested for reactivity with autologous sera sampled over time. The V3 region undergoes immune escape through mutation.


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[Moore & Ho(1995)] J. P. Moore & D. D. Ho. HIV-1 neutralization: the consequences of adaptation to growth on transformed T-cells. *AIDS* 9 suppl A:S117–S136, 1995. This review considers the relative importance of a neutralizing antibody response for the development of an vaccine, and for disease progression during the chronic phase of HIV-1 infection. It suggests that T-cell immunity may be more important. The distinction between MAbs that can neutralize primary isolates, and those that are effective at neutralizing only laboratory adapted strains is discussed in detail. Alternative conformations of envelope and non-contiguous interacting domains in gp120 are discussed. The suggestion that soluble monoclonic gp120 may serve as a viral decoy that diverts the humoral immune response in vivo is put forth.


[Moore & Sodroski(1996)] J. P. Moore & J. Sodroski. Antibody cross-competition analysis of the human immunodeficiency virus type 1 gp120 exterior envelope glycoprotein. *J. Virol.* 70:1863–1872, 1996. OTE: AIDSLINE: 96190589 46 anti-gp120 monomer MAbs were used to create a competition matrix, and MAb competition groups were defined. The data suggests that there are two faces of the gp120 glycoprotein: a face occupied by the CD4BS, which is presumably also exposed on the oligomeric envelope glycoprotein complex, and a second face which is presumably inaccessible on the oligomer and interacts with a number of nonneutralizing antibodies.


[Nilsen et al.(1996)] B. M. Nilsen, I. R. Haugan, K. Berg, L. Olsen, P. O. Brown, & D. E. Helland. Monoclonal antibodies against human immunodeficiency virus type 1 integrase: epitope mapping and differential effects of integrase activities in vitro. *J Virol* 70:1580–1587, 1996. OTE: MEDLINE: 96190555 In this study, 17 anti-integrase murine Mabs were generated and epitopes were mapped by deletion mutations and peptide scanning. The ability of MAb binding to inhibit (or stimulate) end-processing, DNA joining, reintegration, and disintegration enzyme functions in vitro was determined.

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[Otteken et al.(1992)] A. Otteken, S. Nick, W. Berger, G. Voss, A. Faisst, C. Stahl-Hennig, & G. Hunsmann. The carboxyl-terminal region of HIV-1 nef protein is a cell surface domain that can interact with CD4+ T cells. *J. Immunol.* **153**:5826–5837, 1994. OTE: MEDLINE: 95081631 This study shows that the C-terminal end of Nef is accessible to Abs. This domain could bind in a soluble form to CD4+, infected cells, and this interaction is inhibited in the presence of the C-terminal specific antibodies. Syncytium formation was reduced by these Abs or peptides. Abs could stain IIIB/M10, but not MN/M10, infected cells, in a membrane immunofluorescence assay.  


[Pincus et al.(1991)] S. H. Pincus, R. L. Cole, E. M. Hersh, D. Lake, Y. Masuho, P. J. Durda, & J. McClure. In vitro efficacy of anti-HIV immunotoxins targeted by various antibodies to the envelope protein. *J. Immunol.* **146**:4315–4324, 1991. OTE: MEDLINE: 91250725 Six MAbs, (907, 924, 110.1, 41.1, 86 and P5-3) and polyclonal pooled serum antibodies purified on gp160 were coupled to RAC to create immunotoxins. Only 41.1-RAC, an anti-gp41 MAb-immunotoxin and the polyclonal immunotoxin showed direct activity against multiple strains, and activity of an immunotoxin was found not to be directly correlated with cell surface binding.  


[Poignard et al.(1996a)] P. Poignard, T. Fouts, D. Naniche, J. P. Moore, & Q. J. Sattentau. Neutralizing antibodies to human immunodeficiency virus type-1 gp120 induce envelope glycoprotein subunit dissociation. *J Exp Med* **183**:473–484, 1996a. OTE: AIDSLINE: 96195201 Binding of Anti-V3 and the CD4I neutralizing MAb induces shedding of gp120 on cells infected with the T-cell line-adapted HIV-1 molecular clone Hx10. This was shown by significant increases of gp120 in the supernatant, and exposure of a gp41 epitope that is masked in the oligomer. MAbs binding either to the V2 loop or to CD4BS discontinuous epitopes do not induce gp120 dissociation.
This suggests HIV neutralization probably is caused by several mechanisms, and one of the mechanisms may involve gp120 dissociation.

[Poignard et al.(1996b)] P. Poignard, P. J. Klasse, & Q. J. Sattentau. Antibody neutralization of HIV-1. *Immunol. Today* **17**:239–246, 1996b. Comprehensive review of HIV envelope gp120 and gp41 antibody binding domains, and different cross-reactivity groups of MAbs ability to neutralize primary isolates. The distinction between neutralization of laboratory strains and primary isolates is discussed. The only three epitopes that have confirmed broad neutralization against a spectrum of isolates are gp120 epitopes for IgG1b12 and 2G12, and the gp41 epitope of 2F5.


[Potts et al.(1993)] B. J. Potts, K. G. Field, Y. Wu, M. Posner, L. Cavacini, & M. White-Scharf. Synergistic inhibition of HIV-1 by CD4 binding domain reagents and V3-directed monoclonal antibodies. *Virology* **197**:415–419, 1993. OTE: MEDLINE: 94025592 Four anti-V3 loop MAbs, (59.1, 83.1, 50.1, and 58.2), were evaluated for their affinity, neutralization potencies, and their ability to synergize F105 or sCD4 neutralization. The most important parameter for synergy was the capacity to neutralize a given virus independently.


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[Schutten et al.(1993)] M. Schutten, A. McKnight, R. C. Huisman, M. Thali, J. A. McKeating, J. Sodroski, J. Goudsmit, & A. D. Osterhaus. Further characterization of an antigenic site of HIV-1 gp120 recognized by virus neutralizing human monoclonal antibodies. AIDS 7:919–923, 1993. OTE: MEDLINE: 93633254 Three human anti-CD4 binding site MAbs were characterized. Amino acid substitutions that block MAb binding were similar but slightly different than those found in murine anti-CD4 binding site MAbs.


[Spear et al.(1993)] G. T. Spear, D. M. Takefman, B. L. Sullivan, A. L. Landay, & S. Zolla-Pazner. Complement activation by human monoclonal antibodies to human immunodeficiency virus. J. Virol. 67:53–59, 1993. OTE: MEDLINE: 93100837 This study looked at the ability of 16 human MAbs to activate complement. MAbs directed against the V3 region could induce C3 deposition on infected cells and virolysis of free virus, but antibodies to the CD4BS and C-terminal region and two regions in gp41 could induce no complement mediated effects. Pre-treatment with sCD4 could increased complement-mediated effects of anti-gp41 MAbs, but decreased the complement-mediated effects of V3 MAbs. Anti-gp41 MAbs were able to affect IIIB but not MN virolysis, suggesting spontaneous shedding of gp120 on IIIB virions exposes gp41 epitopes. IgG isotype did not appear to have an effect on virolysis or C3 deposition.


[Sullivan et al.(1995)] N. Sullivan, Y. Sun, J. Li, W. Hofman, & J. Sodroski. Replicative function and neutralization sensitivity of envelope glycoproteins from primary and T-cell line-passage human immunodeficiency virus type 1 isolates. J. Virol. 69:4413–4422, 1995. OTE: AIDSLINE: 95287498 Three gp120 molecules derived from primary isolates were compared to T-cell adapted lines HXBc2 and MN. Complementation experiments showed viral entry into peripheral blood mononuclear cell targets was five-fold less efficient for primary isolates. Anti-CD4 binding site neutralizing MAbs were far less potent against primary isolates, and the single anti-V3 MAb tested was 3-fold less potent. The differences in neutralization efficiency could not be attributed to differences in affinity for monomeric gp120, but were related to binding to the oligomeric complex. Enhanced
infectivity of primary isolates was observed using sCD4 and MAb F105, which can neutralize T-cell adapted 
strains.

human immunodeficiency virus type 1 neutralization and infection enhancement by human monoclonal 
receptors for IgG on monocytic cells can serve as a means for MAb mediated enhancement of HIV-1 infection. 
MAbs N70-1.5 and N70-2.3a bind distinct discontinuous epitopes in gp120. N70-1.5 is a potent neutralizing MAb 
with no enhancing activity, while N70-2.3a doesn’t neutralize and mediates enhancement of HIV-1 infection.

Enhanced in vitro human immunodeficiency virus type 1 replication in B cells expressing surface antibody to 
as a surface anti-gp41 monoclonal antibody receptor for gp41 (slg/gp41) by transfection into a CD4-negative 
B-cell line. Transfected cells could bind HIV envelope, but could not be infected by HIV-1. When CD4 delivered 
by retroviral constructs was expressed on these cells, they acquired the ability to replicate HIV-1, and slg/gp41 
specifically enhanced viral replication.

[Teeuwen et al.(1990)] V. J. Teeuwen, K. H. Siebelink, S. Crush-Stanton, B. Swerdlow, J. J. Schalken, 
J. Goudsmit, R. v. Akker, M. J. Stukart, F. G. Uytdehaag, & A. D. Osterhaus. Production and characteri-
zation of a human monoclonal antibody, reactive with a conserved epitope on gp41 of human immunodeficiency 

virus-infected T cells and monocytes are killed by monoclonal human anti-gp41 antibodies coupled to ricin A 

antibodies against the putative CD4 binding site and the V3 loop of HIV gp120 act in concert to neutralize virus. 

J. Robinson, P. J. Maddon, & J. P. Moore. CD4-dependent, antibody-sensitive interactions between HIV-1 and 
HIV-1 strains of the non-syncytium-inducing (NSI) phenotype with CD4+ T-cells. CD4 binding greatly increases 
the efficiency of gp120-CCR-5 interaction. Neutralizing MAbs against the V3 loop and CD4-induced epitopes 
on gp120 inhibited the interaction of gp120 with CCR-5, without affecting gp120-CD4 binding.

immunodeficiency virus type 1 gp120 V3 loop and human brain proteins. J. Virol. 67:7711–7715, 1993. OTE: 
MEDLINE: 94043798.

tan, B. Wang, A. Sato, W. V. Williams, & D. B. Weiner. Generation of monoclonal antibodies against the amino terminus of 
gp120 that elicit antibody-dependent cellular cytotoxicity. Cold Spring Harbor Laboratory Press, Cold Spring 

D. L. Bixr. Dissociation rate of antibody-gp120 binding interactions is predictive of V3-mediated neutralization 
was found that the rate of the dissociation of the MAb-gp120 complex, but not the association rate, correlated 
with MAbs ability to neutralize homologous virus (measured by 50% inhibition of p24 production). Association 
constants were similar for all MAbs tested, varying less than 4-fold. Dissociation rate constants were quite 
variable, with 100-fold differences observed.

for distinct contributions of heavy and light chains to restriction of antibody recognition of the HIV-1 principal 

[Wu et al.(1993)] J. Wu, E. Amandoron, X. Li, M. A. Wainberg, & M. A. Parniak. Monoclonal antibody-mediated 
MEDLINE: 9325974.
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