Antibodies with Distinct Specificities Neutralize Diverse HIV-1 Variants

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The quest to design an effective HIV vaccine is one of medical science's most important current goals. According to the 2011 UNAIDS *World Aids Day Report*, 34 million people were living with HIV at the end of 2010, and 1,700,000 AIDS-related deaths occurred worldwide the same year. Unfortunately, vaccines against HIV-1, the most prevalent and pathogenic type of HIV, have proven difficult to develop because HIV is highly mutable and evolves rapidly in response to host immune defenses. Moreover, the different viruses that arise from this process are extremely variable in molecular structure. This variability extends to the viral envelope glycoprotein, gp120, which mediates HIV-1 entry into $CD4^+$ cells of the human immune system. In a recent report in the *Journal of Virology*, graduate student Leslie Goo, senior author Dr. Julie Overbaugh (Human Biology Division) and two of their colleagues show how a combination of monoclonal antibodies (mAbs) recognizing distinct regions (or 'epitopes') of gp120 may help pave a way toward the eventual creation of a vaccine against HIV-1.

Development of an effective HIV-1 vaccine requires that researchers first establish which HIV-1 variants are most commonly transmitted and are thus more likely to cause new infections. Only then can they examine whether a vaccine candidate induces an immune response that targets *transmitting* viruses. Previous work in Dr. Overbaugh's laboratory has already established that genetic bottlenecks occur during horizontal HIV-1 transmission between sexual partners, as well as during vertical transmission between infected mothers and their infants. These bottlenecks limit the number of HIV-1 viruses that enter a new host (*e.g.*, seeWu *et al.*, 2006).

Building upon these prior advances, Goo *et al.* tested a battery of seven mAbs for their effectiveness in neutralizing 45 HIV-1 envelope variants representing diverse viral subtypes, all of which had been isolated from patients soon after heterosexual transmission [median time post-infection = 59 days]. The investigated mAbs included those targeting the CD4 binding site of gp120 (*e.g.*, mAb NIH45-46W) and those recognizing a glycan-dependent epitope in the third variable loop (V3) of gp120 (*e.g.*, PGT121 and PGT128). The ability of each antibody to neutralize a particular HIV-1 variant was tested in HeLa cells that have been engineered to express the HIV-1 receptors needed for HIV-1 entry. The engineered cells also express a firefly reporter protein upon infection, which allows for the identification and quantification of infected cells by luminescence.

Using this neutralization assay, the authors found that the single most effective mAb was NIH45-46W, which neutralized 91% of HIV-1 variants at a mean effective concentration (IC50) of 0.09 µg/ml (see figure). Although PGT121 and PGT128 were more narrowly effective and less potent on average than NIH45-46W, these V3-targetting mAbs neutralized some HIV-1 variants that escaped neutralization by NIH45-46W. Further investigation showed that NIH45-46W, PGT121 and PGT128 complemented each other: Together, these three mAbs neutralized all HIV-1 variants tested. In a related study in the Overbaugh Lab, which is being conducted by Jennifer Mabuka-Maroa in collaboration with Leslie Goo and Maxwel Majiwa-Omenda, this same combination of mAbs has been found to neutralize 100% of HIV-1 variants that were transmitted vertically from mothers to infants.

It is clear that many challenges still must be overcome if multi-mAb therapies or vaccinations are to be used to prevent HIV transmission. Infusions of mAbs to prevent vertical transmission during childbirth – for example, in high-risk cases – would be far too expensive for much of the world, and it remains unclear if vaccination could induce the desired suite of antibody specificities. Despite these difficulties, however, there is reason to be hopeful: Broadly-neutralizing antibodies targeting both the CD4 binding site and the V3 region of gp120 have been seen to develop in some HIV-infected patients (*e.g.*, Klein *et al.*, 2012). In light of such promising reports, the recent results from the Overbaugh Lab provide an important roadmap for future progress toward an eventual HIV-1 vaccine. They inform us that it should be profitable to focus immunogen design simultaneously on the CD4 binding site and one or more glycan-dependent epitopes in V3.

Goo L, Jalalian-Lechak Z, Richardson BA, Overbaugh J. 2012. A combination of broadly neutralizing HIV-1 monoclonal antibodies targeting distinct epitopes effectively neutralizes variants found in early infection. *J. Virol.* Epub ahead of print, doi:10.1128/JVI.01414-12.

Also see: Wu X, Parast AB, Richardson BA, Nduati R, John-Stewart G, Mbori-Ngacha D, Rainwater SM, Overbaugh J. 2006. Neutralization escape variants of human immunodeficiency virus type 1 are transmitted from mother to infant. *J. Virol.* 80:835-44.

Klein F, Gaebler C, Mouquet H, Sather DN, Lehmann C, Scheid JF, Kraft Z, Liu Y, Pietzsch J, Hurley A, Poignard P, Feizi T, Morris L, Walker BD, Fätkenheuer G, Seaman MS, Stamatatos L, Nussenzweig MC. 2012. Broad neutralization by a combination of antibodies recognizing the CD4 binding site and a new conformational epitope on the HIV-1 envelope protein. *J. Exp. Med.*209:1469-1479

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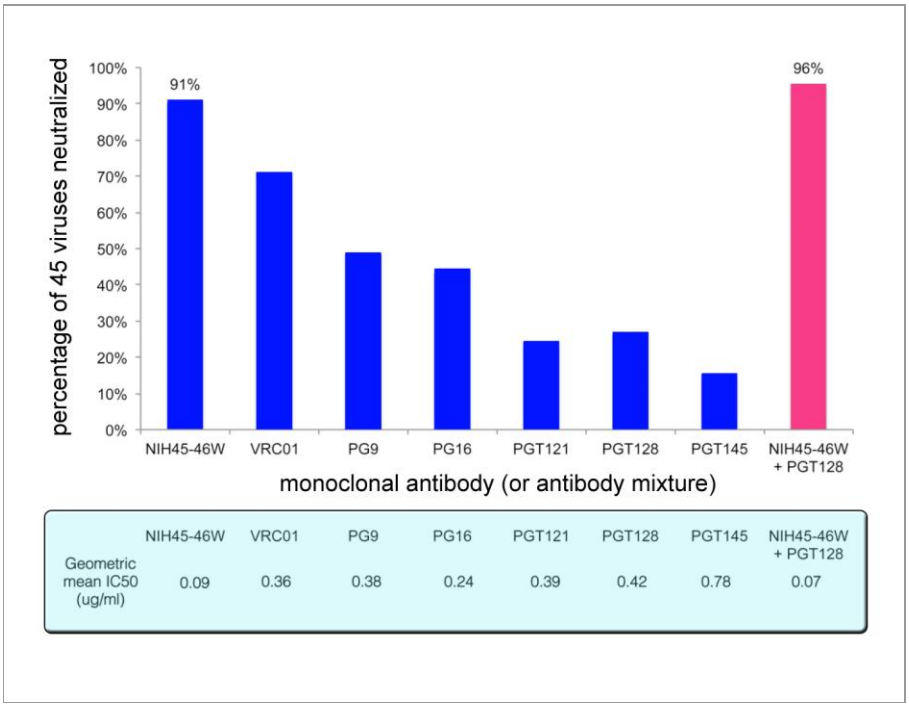

Adapted from the manuscript

Neutralization breadth and potency of monoclonal antibodies against 45 recently transmitted HIV-1 variants. The bar graph, above, shows the percentage of viruses neutralized by each of seven individual antibodies (blue bars) or a mixture of two antibodies (red bar). The shaded blue box, below, gives the geometric means of IC50 values across virus subtypes.