

# OPENING A WINDOW OF VULNERABILITY IN HIV-1

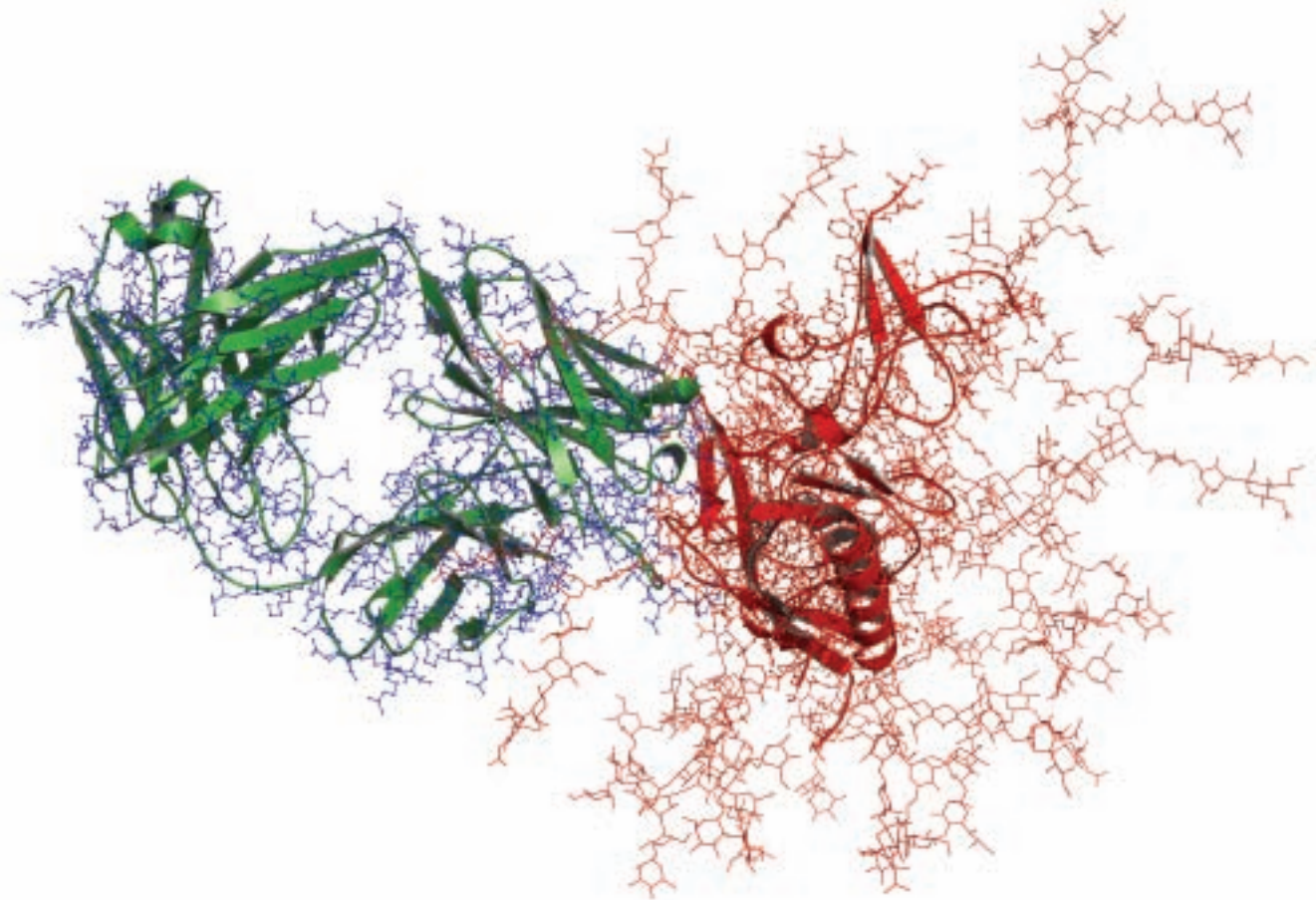


Fig. 1. Representation of the three-dimensional protein structure of the b12 neutralizing antibody in complex with gp120 from HIV-1. A ribbon diagram of the structure of b12 is shown in green with the amino acid side chains for b12 overlaid in blue. The gp120 structure is shown in red with amino acid side chains and glycans for gp120 overlaid, also in red.

**H**IV-1, the virus that causes the acquired immune deficiency syndrome, or AIDS, is a global health problem that has confounded vaccine researchers for many years. One of the things that makes HIV-1 so tricky is its remarkable ability to evade our immune system, in part by changing the three-dimensional appearance of its outer-envelope glycoprotein, gp120. This protein protrudes from the virus and binds to a host molecule called CD4 that makes it possible for the virus to gain entry into cells. This interaction is crucial to persistence of the infection and represents a good target for vaccine intervention. However, HIV-1 has eluded previous vaccination attempts because of its ability to mutate very quickly and change the way gp120 looks to the immune system, making it hard to track. Researchers used the SER-CAT 22-ID-D beamline at the APS to uncover new information that could represent a significant leap forward in HIV vaccine research.

In an attempt to identify a conserved feature of gp120 that might be used to generate a vaccine-stimulated immune response, the researchers from the National Institute of Allergy and Infectious Diseases, Scripps Research Institute, the Dana Farber Cancer Institute, and the National Cancer Institute used a clue from HIV-1-infected individuals who had shown some resistance to the virus. Scientists had found that some of these individuals were generating what were termed “broadly neutralizing” antibodies that presumably recognize an invariant part of the virus. One of these broadly neutralizing antibodies, called b12, appears to recognize an area of gp120 that is involved in the contact the virus makes with CD4. By using the 22-ID-D beamline, this research team achieved an important advance by solving the structure of the b12 antibody binding site to gp120 to a resolution of 2.3 Å. The structure reveals a vulnerable area where b12 can gain access to gp120 and prevent its interaction with host CD4 molecules.

The structure of the interaction between the neutralizing antibody, b12, and viral gp120 has been sought for some time, but the flexibility of the gp120 molecule made it difficult to capture the interaction in crystals of sufficient quality for this type of analysis. By using a trick to stabilize the interaction (trapping gp120 in the conformation it uses to bind CD4), the researchers were able to obtain a snapshot of the interaction (Fig. 1). The team credits APS high-brightness undulator x-ray beams for enabling this finding. The gp120-containing crystals were often quite small (needles with dimen-

sions as small as 20  $\mu\text{M}$ ) and the cell constants were large (dimensions of up to 200 Å). Despite this, data were collected to at least 3-Å resolution for all of the 10 structures required to complete the analysis. Indeed, the analysis revealed important aspects of the interaction between b12 and gp120, showing that b12 binds gp120 in a region that is required for initial contact with CD4.

The implications of the work for vaccine research are significant. In general, vaccination is based on the principal of “teaching” or “priming” the immune system to recognize an invader by using a harmless form of the invader to generate an initial response. This gives the body a chance to identify the invader and generate both a memory of and a neutralizing response to it. When the body is challenged again with the real invader, it is ready with a full arsenal of memory cells to mount a full and rapid response. Previous attempts to use the whole gp120 protein as a vaccine have been foiled by the general variability of the molecule. The structural map of b12 binding to this conserved region of gp120 will allow vaccine researchers to design a structural analog of the vulnerable site to teach the immune system how to generate an effective neutralizing response. — *Sandy Field*

**See:** Tongqing Zhou<sup>1</sup>, Ling Xu<sup>1</sup>, Barna Dey<sup>1</sup>, Ann J. Hessel<sup>3</sup>, Donald Van Ryk<sup>2</sup>, Shi-Hua Xiang<sup>4</sup>, Xinzheng Yang<sup>4</sup>, Mei-Yun Zhang<sup>5</sup>, Michael B. Zwick<sup>3</sup>, James Arthos<sup>2</sup>, Dennis R. Burton<sup>3</sup>, Dimiter S. Dimitrov<sup>5</sup>, Joseph Sodroski<sup>4</sup>, Richard Wyatt<sup>1</sup>, Gary J. Nabel<sup>1</sup>, and Peter D. Kwong<sup>1\*</sup>, “Structural definition of a conserved neutralization epitope on HIV-1 gp120,” *Nature* **445**, 732 (15 February 2007).

DOI: 10.1038/nature05580

**Author affiliations:** <sup>1</sup>Vaccine Research Center, and <sup>2</sup>Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health; <sup>3</sup>Departments of Immunology and Molecular Biology, Scripps Research Institute; <sup>4</sup>Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School; <sup>5</sup>Center for Cancer Research, National Cancer Institute

**Correspondence:** \*pdkwong@nih.gov

Support for this work was provided by the Intramural Research Program of the NIH, by the International AIDS Vaccine Initiative, by a grant from the Bill and Melinda Gates Foundation Grand Challenges in Global Health Initiative, and by grants from the NIH. Use of the APS was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357.

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