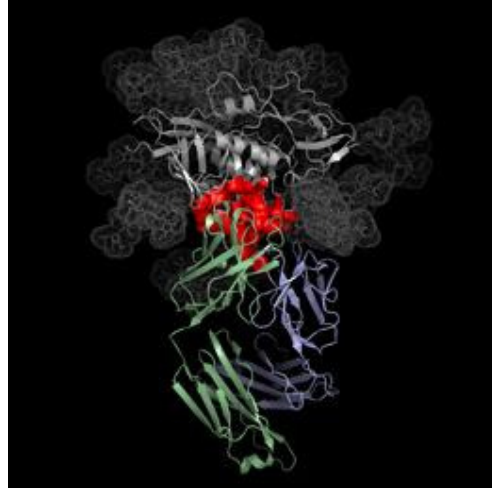


## Souped-up antibody fends off HIV

Targeted search yields proteins that neutralize nearly all HIV strains.

Heidi Ledford



VRC01, coloured green and blue here, neutralizes the vast majority of HIV-1 strains.

*Peter Kwong, Jonathan Stuckey,  
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An antibody that can block more than 90% of strains of HIV-1, the most common form of the disease, has been discovered using a method for fishing specific proteins out of the blood. The findings, published today in *Science*<sup>1,2</sup>, could be used for vaccine design, researchers say.

It is the latest step in the quest to find a 'broadly neutralizing' antibody, capable of blocking a large quantity of the many HIV-1 strains known around the world. The past year has brought a spate of HIV-1 antibody discoveries, including the report last September of a set of antibodies that could target up to 78% of HIV strains<sup>3</sup> (see 'Fresh targets give hope for HIV vaccine').

"Knowing that it's possible for a human to make this kind of antibody really increases our optimism that it could be elicited by a vaccine," says Gary Nabel, a virologist at the National Institute of Allergy and Infectious Diseases' Vaccine Research Center in Bethesda, Maryland, who is a co-author on the two new *Science* papers.

"Clearly the neutralizing-antibody field for HIV-1 is hotting up," says Robin Weiss, a virologist at University College London.

The results have been exciting, Weiss adds, because they address lingering concerns that antibodies against HIV-1 may need to be very specific — targeting only a few strains — if they are to be potent. "Our overall thinking has changed in light of these recent papers," he says.

## Unique structures

Although several antibodies against HIV-1 have previously shown promise, they were often structurally unusual in ways that confound vaccine designers. One region of an antibody might be unusually long, or contain a certain chemical modification — features that researchers do not know how to generate in the body using a vaccine.

"Antibodies are like people: every single one is unusual in its own specific way," says Peter Kwong, a structural biologist at the Vaccine Research Center, and a co-author on both papers.

**"These antibodies are freaks of nature."**

In seeking better antibodies against HIV-1, Nabel, Kwong and their colleagues confronted another challenge: antibodies that broadly neutralize against HIV-1 are extremely rare. Kwong compares the search to looking for diamonds in a pile of cubic zirconia: "If you're simply picking up pretty rocks, you'll never find them," he says.

Instead, the team designed a probe to specifically pick out antibodies that act against the part of the virus's protein envelope that interacts with the cells targeted by HIV, called CD4<sup>+</sup> cells. Other regions of the envelope that might stimulate an immune response were masked by replacing them with sequences from other viruses to reduce the odds of fishing out unwanted antibodies<sup>1</sup>.

The team screened 25 million antibody-producing white blood cells, called B cells, from 15 people with HIV-1, searching for those that bound to their probe. Only 29 cells fit the bill. From those, the researchers isolated three broadly neutralizing antibodies.

Structural analysis of one of the antibodies, named VRC01, showed that it almost exactly mimics the binding of the virus to a CD4<sup>+</sup> cell, but for a slight 6-ångström shift and a 43° rotation<sup>2</sup> — roughly the difference in the position of the hour hand on a clock between midnight and 1:30, Kwong says.

## New hope, new challenges

The antibody does present its own challenges to vaccine design, however. As the body continues to produce antibodies against a disease, the B cells undergo several rounds of mutation and subsequent selection for those antibodies that best bind their target. This process is called affinity maturation.

As a result, most mature antibodies will harbour about 10—15 mutations, says Kwong. VRC01 had 66.

The team found that an 'immature' form of the antibody, without the mutations, was not able to block HIV-1.

A vaccine based on this work would have to stimulate the body to produce antibodies like VRC01. At present, researchers do not fully understand how this maturation process works, making it difficult to design a vaccine that would harness it appropriately. Nabel speculates that such a vaccine may need to be given repeatedly, to foster the production of more mature, heavily mutated antibodies, and could even consist of different components at different stages — one given to stimulate the generation of the basic VRC01 backbone, and another administered later to select a specific 'mature' form of the antibody.

The antibodies could also be used directly in HIV-infected patients as an alternative to anti-retroviral therapy, notes Nabel. But such a therapy would have to be shown to be more effective than existing drugs to warrant the added expense and difficulty of administering an antibody-based therapy.

Another important step before developing a VRC01-based vaccine is to check whether most people can generate such antibodies or only a select few. The team is looking for the antibodies in other patients, and thus far the results are promising, says Kwong.

If those details are worked out, says Nabel, combining vaccines that elicit the VRC01 antibody with those that yield other broadly neutralizing antibodies could potentially inhibit nearly all strains of HIV and hinder the capricious virus's ability to evolve an escape route. "A nice cocktail of three or so would give us a good chance of containing the virus," he says.

## References

1. Wu, X. *et al.* Science doi:10.1126/science.1187659 (2010).
2. Zhou, T. *et al.* Science doi:10.1126/science.1192819 (2010).
3. Walker, L. M. *et al.* Science 326, 285-289 (2009).