Biologists create anti-HIV antibody that shows increased potency

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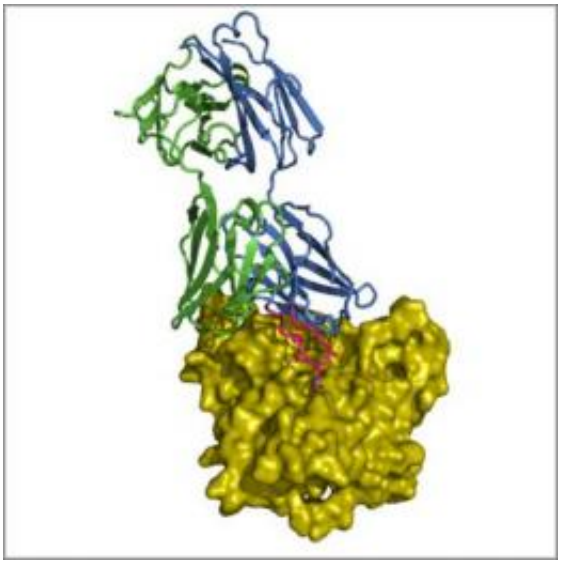

The increased potency of a new HIV antibody (green and blue), is explained by an insertion (pink) that contacts the inner domain of the HIV gp120 spike protein (yellow). Credit: Ron Diskin/California Institute of Technology

Using highly potent antibodies isolated from HIV-positive people, researchers have recently begun to identify ways to broadly neutralize the many possible subtypes of HIV. Now, a team led by biologists at the California Institute of Technology (Caltech) has built upon one of these naturally occurring antibodies to create a stronger version they believe is a better candidate for clinical applications.

Current advances in isolating antibodies from HIV-infected individuals have allowed for the discovery of a large number of new, broadly neutralizing anti-HIV antibodies directed against the host receptor (CD4) binding site—a functional site on the surface of the virus that allows for cell entry and infection. Using a technique known as structure-based rational design, the team modified one already-known and particularly potent antibody—NIH45-46—so that it can target the binding site in a different and more powerful way. A study outlining their process was published in the October 27 issue of *Science Express*.

"NIH45-46 was already one of the most broad and potent of the known anti-HIV antibodies," says Pamela Bjorkman, Max Delbrück Professor of Biology at Caltech and senior author on the study. "Our new antibody is now arguably the best of the currently available, broadly neutralizing anti-HIV antibodies."

By conducting structural studies, the researchers were able to identify how NIH45-46 interacted with gp120—a protein on the surface of the virus that's required for the successful entry of HIV into cells—to neutralize the virus. Using this information, they were able to create a new antibody (dubbed NIH45-46G54W) that is better able to grab onto and interfere with gp120. This improves the antibody's breadth—or extent to which it effectively targets many subtypes of HIV—and potency by an order of magnitude, according to Ron Diskin, a postdoctoral scholar in Bjorkman's lab at Caltech and the paper's lead author.

"Not only did we design an improved version of NIH45-46, our structural data are calling into question previous assumptions about how to make a vaccine in order to elicit such antibodies," says Diskin. "We hope that these observations will help to guide and improve future immunogen design."

By improving the efficacy of antibodies that can neutralize HIV, the researchers point to the possibility of clinical testing for NIH45-46G54W and other antibodies as therapeutic agents. It's also plausible that understanding effective neutralization by powerful antibodies may be useful in vaccine development.

"The results uncover the structural underpinnings of anti-HIV antibody breadth and potency, offer a new view of neutralization by CD4-binding site anti-HIV antibodies, and establish principles that may enable the creation of a new group of HIV therapeutics," says Bjorkman, who is also a Howard Hughes Medical Institute investigator.

More information: "Increasing the Potency and Breadth of an HIV Antibody by Using Structure-Based Rational Design," *Science Express*.

Provided by California Institute of Technology