Piece of HIV protein may be key to AIDS vaccine development

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In a finding that could have profound implications for AIDS vaccine design, researchers led by a team at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, have generated an atomic-level picture of a key portion of an HIV surface protein as it looks when bound to an infection-fighting antibody. Unlike much of the constantly mutating virus, this protein component is stable and—more importantly, say the researchers—appears vulnerable to attack from this specific antibody, known as b12, that can broadly neutralize HIV.

"Creating an HIV vaccine is one of the great scientific challenges of our time," says NIH Director Elias A. Zerhouni, M.D. "NIH researchers and their colleagues have revealed a gap in HIV's armor and have thereby opened a new avenue to meeting that challenge."

The research team was led by Peter Kwong, Ph.D., of NIAID's Vaccine Research Center (VRC). His collaborators included other scientists from NIAID and the National Cancer Institute, NIH, as well as investigators from the Dana-Farber Cancer Institute, Boston, and The Scripps Research Institute in La Jolla, CA. Their paper appears in the February 15 issue of *Nature* and is now available online.

"This elegant work by Dr. Kwong and his colleagues provides us with a long-sought picture of the precise interaction between the HIV gp120 surface protein and this neutralizing antibody," says NIAID Director Anthony S. Fauci, M.D. "This finding could help in the development of

an HIV vaccine capable of eliciting a robust antibody response."

For years, AIDS vaccine developers have been stymied by the seemingly unlimited ways HIV eludes natural and vaccine-induced immune defenses. Notes Dr. Kwong, "The more we learned about HIV, the more we realized just how many levels of defense the virus has against attacks by the immune system." For example, not only does HIV mutate rapidly and continuously—defeating attempts by the immune system to identify and destroy it—the virus is also swathed by sugary molecules. This nearly impenetrable sugar cloak prevents antibodies from slipping in and blocking the proteins the virus uses to latch onto a cell and infect it.

In 1998, Dr. Kwong and colleagues published the first X-ray snapshot of the core of HIV gp120 as it attaches to a cellular receptor known as CD4. That image gave researchers a glimpse of some sites on the virus that could be targets of drugs or vaccines, but it also revealed the extent of HIV's overlapping defenses. For example, scientists subsequently learned that CD4-gp120 contact causes gp120 to change shape, a viral feint known as conformational masking, which acts to further shield HIV from immune system attack.

While the earlier study provided a picture of the CD4-gp120 complex, the new finding delineates the precise stepwise engagement between gp120 and CD4. The researchers found that the gp120-CD4 encounter starts with a highly focused contact and then expands to a broader surface that stabilizes the interaction.

"The first contact is like a cautious handshake, which then becomes a hearty bear hug," says Gary Nabel, M.D., Ph.D., director of NIAID's VRC and co-author of the new paper.

An effective HIV vaccine likely needs to induce antibodies that can sense and destroy multiple HIV strains. Scientists have sought such

broadly neutralizing antibodies by studying the blood of people whose immune systems appear to hold the virus at bay for long periods of time—b12 is one of these rare, broadly neutralizing antibodies.

Until now, no one had succeeded in determining the detailed structure of b12 in complex with gp120. It was extremely difficult to crystallize b12 bound to gp120, says Dr. Kwong, in part due to the inherently flexible nature of the chemical bonds in gp120. To overcome the problem, the investigators created a variety of gp120s and eventually made the protein stiff enough to capture a picture of it in complex with b12. They saw that b12 binds gp120 at the same point where gp120 initially attaches to CD4. Unlike the gp120-CD4 interactions, however, b12 can latch onto the site of CD4's first contact without requiring a shape change in gp120 to create a stable bond between the two molecules. Essentially, the scientists found that the initial point of CD4 contact is a site of gp120 weakness because it is the site of recognition—called an epitope—for b12.

"One of our primary goals is to develop HIV vaccines that can stimulate broadly neutralizing antibodies," says Dr. Nabel. "The structure of this gp120 epitope, and its susceptibility to attack by a broadly neutralizing antibody, shows us a critical area of vulnerability on the virus that we may be able to target with vaccines. This is certainly one of the best leads to come along in recent years."

Source: National Institute of Allergy and Infectious Diseases