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"Natural" Strategy May Improve HIV Vaccines

Researchers say a new HIV vaccine development strategy has emerged from the first in-depth studies of memory B cells produced by certain people whose immune systems make antibodies that can resist HIV infection. The new idea is to create a vaccine that would induce the body to produce a "swarm" of natural antibodies that launch multiple attacks against HIV infection.

By contrast, current HIV vaccines are designed to induce the immune system to produce one of a number of artificially engineered "super antibodies" against a range of strains of HIV. However, experimental vaccines so far have not been able to induce production of these super antibodies

Howard Hughes Medical Institute (HHMI) investigator Michel C. Nussenzweig and his colleagues, including HHMI investigator Bruce D. Walker, reported their findings March 15, 2009, in an advance online publication in the journal *Nature*. Johannes Scheid, a student in Nussenzweig's laboratory at The Rockefeller University, was the first author of the research article. Walker is at Massachusetts General Hospital and Harvard Medical School.

Antibodies are infection-fighting proteins produced by long-lived memory B cells in the immune system. Each memory B-cell harbors the genetic blueprint for producing a specific antibody. Earlier studies of HIV-infected patients by Walker and others revealed that about 10 percent of people infected with HIV are so-called "elite controllers," whose immune systems keep the HIV viral load to below 50 virus particles per milliliter of blood. The average untreated patient with HIV infection has a viral load of more than a million particles at the time of acute infection. Viral load is what dictates, to a large extent, whether a person gets sick or transmits disease.

Despite the fact that researchers had identified elite controllers some time ago, little was known about their antibodies because it had not been possible to isolate the memory B cells responsible for making them, said Nussenzweig.

In a key technical advance reported in the *Nature* article, Scheid developed a technique for isolating the responsible memory B cells. Using that technique, he isolated HIV-specific memory B cells from the blood of six HIV-infected

elite controllers with high titers of broadly neutralizing antibodies. Scheid identified B cells whose antibodies attack the gp140 protein, a spike-shaped protein that pokes out from the surface of the HIV virus. HIV uses gp140 to harpoon and later attach itself to the immune cells it invades. The spike has been a prime target of HIV drug development efforts because its structure is one of the few things the HIV virus is not able to change through mutation.

Once they had sifted out the memory B cells, the researchers used genetic techniques to manufacture the anti-HIV antibodies that these B cells produce. Testing these antibodies against the virus, they discovered that, while individual antibodies did not neutralize broadly, collectively they neutralized many different viral strains.

“What we found is what I think an immunologist might expect—that the antibody system is doing everything that it can in order to deal with the virus,” said Nussenzweig. “It is not that the virus has one little place that the antibody likes. The antibody system is trying to attack the virus from every different angle. What is interesting about our findings is that it takes all of that in order to broadly neutralize the virus.”

Such a broad attack is critical, said Nussenzweig, “because HIV is constantly mutating in different individuals. So if you make an antibody to HIV that protects against one strain, it is not going to help in terms of a vaccine because every individual has a different HIV.”

Nussenzweig said that the findings could have important implications for vaccine design strategy. “It would seem more productive from our findings to get away from trying to reproduce a single antibody and to work toward a natural global vaccine that would aim to reflect how individuals that produce high titers of broadly neutralizing antibodies can do so,” he said. However, said Nussenzweig, further studies of this natural response will be necessary to establish its universality.

“We need to know which mixtures of antibodies can be most broadly protective,” he said. “Also, we would like to study other HIV viral groups, or clades, and many individuals, not just elite controllers. If we find that our findings regarding these antibodies are generalizable, it would make a very strong case that they could be the basis for trying to create a successful vaccine,” he said.

Nussenzweig and his colleagues at Rockefeller collaborated on the studies with researchers from Charité Universitätsmedizin in Germany, Beth Israel Deaconess Medical Center, Freie Universität Berlin, the National Institutes of Health, Mass General Hospital and Harvard Medical School, Max Planck Institute for Infection Biology in Germany and the Aaron Diamond AIDS Research Center.