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New AIDS Vaccine Approach Aims to Catch Virus in the Act

A novel approach to producing antibodies against the AIDS virus has proven effective against a wide range of HIV strains, raising the hope that a broadly effective vaccine is possible. The new approach generates immune system antibodies against the infective proteins of the virus while the virus is fusing with a target cell.

Scientists from the University of Montana and the Howard Hughes Medical Institute (HHMI) at New York University Medical Center sought to "freeze" the AIDS viral machinery in the act of contorting itself to fuse with its target cell. The investigators believed that this transition stage in the infective process exposes immune-triggering molecules that the virus normally keeps hidden within the depths of its structure.

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— Dan R. Littman

The scientists' success at producing broadly effective antibodies against HIV is in sharp contrast to previous efforts, in which the resulting antibodies neutralized laboratory-grown HIV strains, but not "primary isolates," strains of the virus found in AIDS patients.

Reporting the new findings in the January 15, 1999, issue of the journal *Science* are University of Montana researchers Jack Nunberg, Rachel LaCasse, Kathryn Follis and Meg Trahey; and Dan Littman and John Scarborough of HHMI at New York University Medical Center.

"Perhaps to the surprise of all involved, this ambitious experiment worked," wrote AIDS researchers David Montefiori and John Moore in a commentary on this work that was also published in the January 15 issue of *Science*. "The mouse sera, and antibodies purified from them, inhibited the infectivity of an impressive array of diverse HIV-1 primary isolates, including viruses from

multiple genetic subtypes." Montefiori is at Duke University Medical Center, and Moore is at The Rockefeller University.

Nunberg and his colleagues began by constructing a molecular facsimile of the AIDS infective machinery and of the receptors to which it binds on surface of host cells.

They first genetically engineered monkey cells to produce the HIV surface, or envelope, molecules that are responsible for grabbing onto human cells in the infective process. These surface molecules are called glycoproteins. The researchers then mixed these monkey cells with human cells whose surface was festooned with the receptors that HIV latches onto in infecting cells.

The scientists "froze" the combined cells in the act of fusing by treating them with a weak solution of formaldehyde, which forged a web of chemical links that trapped the molecules in place.

The researchers then injected this mixture, which they dubbed a "fusion-competent immunogen," into mice that Littman's team had genetically engineered to also produce the human receptors. Littman's group had developed the mice specifically to serve as models for HIV vaccine development. Using such mice for immunization was necessary to avoid having the animals' immune system react to the foreign human receptors, rather than to the HIV machinery.

Finally, the Montana scientists isolated an antibody-rich blood serum from the immunized mice. They tested this serum's effectiveness against HIV by mixing it with a diverse collection of viruses isolated from infected humans. The researchers discovered that the antibodies effectively neutralized every one of the many different strains of HIV.

"I think it's a very, very encouraging development," says Littman. "Until now, it has been very difficult to generate antibodies against HIV envelope glycoprotein that are broadly reactive. This is really the first example of being able to somehow trick the immune system into making broadly neutralizing antibodies that are presumably active against the HIV envelope glycoprotein."

Nunberg, Littman and their colleagues emphasize that while the new approach is highly promising, much work remains for the method to prove useful in a vaccine for humans. For one thing, they said, injection of whole live cells into humans is not practical in terms of vaccine safety or durability.

Rather, said Littman, a vaccine will likely depend on isolating the specific glycoprotein that triggers response to HIV and producing it using recombinant DNA technology. "Based on this advance, however, I think there is a good possibility that we'll be able to mimic the immunogenic properties of fusion-competent envelopes on cells by instead using recombinant proteins," he said.

The scientists also said it will be important to determine whether the antibodies they generated in mice can also be generated in primates and, eventually, in humans.