New Approach to Blocking H.I.V. Raises Hopes for an AIDS Vaccine

By DONALD G. McNEIL JR.    FEB. 18, 2015

A new compound has blocked H.I.V. infection so well in monkeys that it may be able to function as a vaccine against AIDS, the scientists who designed it reported Wednesday.

H.I.V. has defied more than 30 years of conventional efforts to fashion a vaccine. The new method stimulates muscle cells to produce proteins that somewhat resemble normal antibodies, which have Y-shaped heads. These proteins have both a head and a tail, and they use them to simultaneously block two sites on each “spike” that the virus uses to attach itself to a cell.

If both sites can be blocked on every spike, the virus becomes helpless and drifts off unattached into eventual oblivion by the immune system.

“lt’s a twofer,” said Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, which supported the work. “lt’s very impressive, and the method is quite promising. But it’s still just in an animal model, so we’ll need to see evidence of whether it works in humans.”

The technique, the paper’s lead author said, has now completely protected four monkeys for nearly a year against repeated attempts to infect them with large doses of several strains of S.H.I.V., a version of H.I.V. adapted for use in lab monkeys.

The author, Michael Farzan, an infectious disease specialist at the Scripps Research Institute in Florida, described the new compound as “the broadest and most potent entry inhibitor described so far.”

It is simpler and works better, he said, than the current method that
scientists are experimenting with: giving monkeys cocktails of several different **antibodies** that each neutralize only one or two strains of H.I.V., sometimes imperfectly.

The study was published online by the journal Nature.

Describing over the telephone the way his new compound worked, Dr. Farzan said he was bending his hand into a claw, with his thumb representing the end blocking one site and two fingers blocking the other.

“One of my colleagues told me it’s the grip for a two-seam cut fastball,” he said.

The work was led by scientists at his institute but involved researchers from Harvard, Princeton, Rockefeller University, the University of Southern California, the Pasteur Institute in France and elsewhere.

The next step, Dr. Farzan said, will be to test the compound in infected monkeys and see if it can stop the virus from replicating further, which is what antiretroviral medicines do. If that proves safe and effective, he said, he hopes to start human trials in three stages.

In the first, humans would be injected every few weeks with just the antibody-like protein, not with the vector that stimulates muscle cells to produce it. If that were successful, the vector would be injected into humans who already have H.I.V. but are not taking antiretroviral pills because they refuse, forget or experience bad side effects.

Finally, the compound would be given to healthy people at high risk — such as gay men who have frequent unprotected sex with strangers — to see if it protects them.

The new approach uses cutting-edge techniques that are not widely known, or even entirely understood, by the scientists experimenting with them.

Historically, vaccines have been made by killing or weakening whole viruses and injecting them; that stimulates the immune system to produce antibodies that recognize and attack the real virus when it arrives.

Newer vaccines splice genes for particular antibodies into other weakened viruses. Generally, the genes are carried into a cell by the virus, incorporated
into the cell’s genome, and begin producing the necessary antibodies.

But this new method splices the desired gene into a stretch of DNA so short that it cannot function like a virus at all and does not deserve to be called one, Dr. Farzan said, who refers to it simply as “a gene therapy vector.” It does not integrate itself into the DNA of a cell or replicate itself. (Yet it is sometimes called an A.A.V., short for “adeno-associated virus,” even though that causes confusion, said Dr. Farzan.)

Nonetheless, injecting that vector into muscle stimulates cells to produce the antibody-like protein encoded by the gene.

“Why? We’re not really able to answer that question,” Dr. Farzan said. “But it does.”

H.I.V. normally targets CD4 cells, white blood cells that act as the sentinels of the immune system.

The virus invades them by attaching its outer spikes — known as envelope proteins — to two different receptors on the outside of the cell. First it attaches to the CD4 receptor; that exposes the CCR5 receptor. Once attached to both, the virus can inject its RNA into the cell and hijack its inner machinery to produce more virus.

But the protein produced by Dr. Farzan, bent into its claw shape, blocks both the CD4-binding site and the CCR5-binding site. It does so in a very tight “match” difficult for the virus to block by means of “escape mutations” — changes in shape that partly prevent engineered antibodies from attaching.

“It fools the virus into thinking it’s interacting with a cell,” Dr. Farzan said.

Dr. Philip R. Johnson, director of the Children’s Hospital of Philadelphia Research Institute and the inventor of the vector that Dr. Farzan used, called the new approach “good stuff.”

“It appears to be as good as, if not better than, anything else that’s being tried,” he said.

Eventually, he said, he would like to see an approach that combined known antibodies and the new protein “so we could target two or three areas on the virus.”
A version of this article appears in print on February 19, 2015, on page A17 of the New York edition with the headline: New Approach to Blocking H.I.V. Raises Hopes for an AIDS Vaccine.

© 2015 The New York Times Company