New HIV vaccine approach targets desirable immune cells

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Researchers at Duke University Medical Center, Beth Israel Deaconess Medical Center and Harvard Medical School have demonstrated an approach to HIV vaccine design that uses an altered form of HIV's outer coating or envelope protein.

The researchers showed that they could design HIV envelopes that could bind better to immature B cell receptors to create an enhanced immune response in an animal model. Immature B cells are the targets of vaccines, and when strongly targeted, they produce strong vaccine responses. The work of the Duke team was to improve on the ability of the HIV envelope to target immature B cells of the immune system.

"This is first step towards a new way of making vaccines against HIV: targeting immature immune cells and attempting to drive a pathway of events that rarely occur," said Barton Haynes, M.D., co-senior author and director of the national Center for HIV-AIDS Vaccine Immunology (CHAVI) laboratory and Frederic M. Hanes Professor of Medicine and Immunology at Duke University School of Medicine. "This avenue of research provides additional evidence about why some of the earlier, traditional vaccine approaches for HIV may not have been successful."

The study was published in the Sept. 1 issue of *PLoS Pathogens*.

Handcrafting vaccines that will stimulate different stages of the pathway toward immunity looks to be important, Haynes said. A vaccine usually uses a part of the virus (like part of its outer coating) or a harmless form

of the virus to create a strong immune response against the virus.

This new work is the first time researchers have made an HIV envelope that binds better to precursor antibodies and also stimulates better immunity, compared with a natural envelope, in primates.

Hua-Xin Liao, M.D., Ph.D., a professor of medicine in the Duke Human Vaccine Institute (DHVI) and co-senior author, created the altered HIV outer coats. "Roadblocks thrown up by HIV have plagued HIV vaccine development," Liao said. "HIV hides its Achilles' heels of vulnerability on its outer coat by covering them with sugars. This covering is the result of virus mutations as the virus became resistant to antibodies."

The researchers found that the sugars on the natural HIV envelope prevented the envelope from binding to the immature B cell receptors that scientists want to trigger with a vaccine. So human and animal B cells fail to make antibodies against the HIV envelope's vulnerable spots when natural HIV envelope is injected as a vaccine candidate, even though these viral envelopes are the target of protective, neutralizing antibodies.

"We found that when you remove the sugars from the envelope proteins, you can create an envelope that targets those immature B cell receptors," said Haynes, who is also director of the DHVI.

"After the initial results, we completed a study in primates, which are similar to humans in terms of their genetics and their immune systems," Haynes said. "When they were given the HIV outer coat with many of the sugars removed, this sugar-depleted envelope bound better to the immature B cell receptors and stimulated antibodies better, which is a first step in the HIV-1 envelope activating an immature B cell target that previously it could not target."

Dimiter Dimitrov at the National Cancer Institute has previously shown that the natural HIV envelope protein frequently does not target immature B cells.

"The importance of this new finding is that it not only provides evidence for our hypothesis, but also for the first time it has identified envelope-based immunogens capable of binding to putative antibody germline predecessors that correlated with enhanced immunogenicity in animals," Dimitrov said.

Investigators have found that pathways for inducing the "right" kind of antibodies may be blocked or are unusual and are not routinely followed by HIV envelope-induced antibodies. John Mascola, Peter Kwong and colleagues at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID) have shown that very complex, broadly neutralizing B cell maturation pathways may require targeting early B cell receptors.

"This is an important step forward," said Nelson Michael, director of the Military HIV Research Program at the Walter Reed Army Institute of Research. "The observation that improving envelope immunogen binding to immature B cell receptors can improve immunogenicity provides new hope for design of strategies for inducing difficult-to-induce neutralizing antibodies."

Norman Letvin, a professor of medicine in immunology at Harvard, performed the envelope immunizations in rhesus macaques. "These new envelope immunogens are the first step towards driving immature B cells through new pathways to make HIV-protective antibodies," Letvin said.

Provided by Duke University Medical Center