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New insights into HIV vaccine will improve drug development

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Four years ago, a potential HIV vaccine showed promise against the virus that causes AIDS, but it fell short of providing the broad protection necessary to stem the spread of disease.

Now researchers—led by Duke Medicine and including team members from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, the U.S. Military HIV Research Program and the Thailand Ministry of Health—have gained additional insights into the workings of the vaccine that help explain why it benefited a third of recipients and left others vulnerable. The findings, reported in the Jan. 10, 2013, issue of the journal *Immunity*, are providing new options for vaccine designers to strengthen the drug.

"This study shows what types of antibodies the vaccine induced and gives us information that can guide the study of future vaccine trials," said senior author Barton Haynes, M.D., director of the Duke Human Vaccine Institute. "Understanding how this vaccine works is important to develop strategies to make it better."

The research team focused on an HIV vaccine candidate tested in Thailand called ALVAC. In 2009, AIDS researchers reported that the vaccine protected 31.2 percent of study participants from HIV infection. It was an encouraging protection rate, but short of the minimum 50-percent efficacy required to slow the epidemic, which afflicts an estimated 34 million people worldwide.

Since that time, researchers have been studying the vaccine for clues to its successes and failures in the hopes of making improvements. Haynes and colleagues reported last year they had found a correlation between a key antibody response to the drug and a lower risk of infection.

"But that was a correlation of risk, not necessarily a correlation of protection," Haynes said. "We couldn't prove that the antibody was the cause of protection."

In the current study, the researchers have strengthened the association between the vaccine-induced antibodies and found crucial characteristics of the antibodies induced by the vaccine. Analyzing the immune responses produced by three vaccine recipients in the original trial, the researchers isolated four key antibodies that targeted an important site on the HIV virus – a region known as V2.

In spite of variations in the V2 site's structure, the antibodies zeroed in on the virus, specifically binding at a position on the virus' outer coating that was already known for attracting immune warriors called neutralizing antibodies.

But the researchers found that the four vaccine-triggered antibodies worked differently than the neutralizing antibodies. Instead of attacking the virus directly, the vaccine-induced antibodies recognized virus-infected cells and flagged them for an attack by other immune cells.

The findings indicate that these types of V2 antibodies expand the immune system's arsenal against HIV, potentially enhancing the effects of the existing ALVAC vaccine.

"The next step for our research is to explore how to design immunogens to induce antibodies that can have broadly neutralizing activities," said Hua-Xin Liao, M.D., PhD, lead author and research director of Duke

Human Vaccine Institute. "Our findings provide new targets for this research."

More information: *Immunity*, Liao et al.: "Vaccine Induction of Antibodies Against a Structurally Heterogeneous Site of Immune Pressure within HIV-1 Envelope Protein Variable Regions 1 and 2." dx.doi.org/10.1016/j.immuni.2012.11.011

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