

Biological catch-22 prevents induction of antibodies that block HIV

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Scientists seeking to understand how to make an AIDS vaccine have found the cause of a major roadblock. It turns out that the immune system can indeed produce cells with the potential to manufacture powerful HIV-blocking antibodies - but at the same time, the immune system works equally hard to make sure these cells are eliminated before they have a chance to mature.

"These studies show that a potentially protective neutralizing antibody against a viral disease is under the control of immunological tolerance," said Barton Haynes, M.D., director of the Center for HIV/AIDS Vaccine Immunology (CHAVI) at Duke University Medical Center and senior author of the study appearing in the online early edition of the [Proceedings of the National Academy of Sciences](#). "This represents a new insight into the way HIV effectively evades detection by the B cell arm of the [immune system](#) and may offer new directions for vaccine design."

Over the years, scientists have assumed that [B cells](#) - one of the first lines of defense against infection - are simply not able to "see" the [HIV virus](#). HIV has the ability to hide its most vulnerable parts from immune system surveillance, and researchers generally assumed that helped explain why B cells often took weeks and even months to arise following infection.

But several years ago, Duke researchers hypothesized that the antibodies required to broadly neutralize HIV may not be produced in the first

place because the immune system "sees" them as a potential threat - due to their similarity to antibodies that promote autoimmune disease - and destroys them.

To see if this is indeed what happens, Laurent Verkoczy, Ph.D., assistant professor of medicine at Duke and the lead author of the study, and Haynes genetically engineered a mouse that could only produce B cells containing a rare but potent broadly neutralizing human antibody that is able to block HIV infection.

Researchers found that the mouse's immune system produced plenty of early stage B cells bearing this human neutralizing antibody on their surface but eliminated most of them before they had a chance to fully evolve into more mature B cells capable of secreting the antibody.

"This work may mean that we need to think and act very differently in envisioning how a successful vaccine may work," said Verkoczy. "The good news is that while about 85 percent of the "right" kind of B [cells](#) are eliminated, about 15 percent survive and wind up in circulating blood, but are turned off. One goal in vaccine design may be to figure out how to wake them up so they can go to work."

"We have now unveiled a major reason why members of this class of neutralizing antibodies are not routinely made: Our own immune systems block their production because they are perceived as potentially harmful, when in reality, they are not," said Haynes. "This is a very unusual way the virus has developed to evade the immune system."

Haynes says researchers plan on using the new mouse model to test ways to teach the immune system to enable the production of powerful neutralizing antibodies capable of blocking [HIV](#).

Provided by Duke University Medical Center

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