Why evolution is the challenge—and the promise—in developing a vaccine against HIV

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To fight HIV, the development of immunization strategies must keep up with how quickly the virus modifies itself. Now, Boston Children's Hospital researchers are developing models to test HIV vaccines on a faster and broader scale than ever before with the support of the Bill & Melinda Gates Foundation.

"The field of HIV research has needed a better way to model the immune responses that happen in humans," says Frederick Alt, PhD, director of the Boston Children's Program in Cellular and Molecular Medicine, who is leading the HIV vaccine research supported by the Gates Foundation.

The researchers are racing against HIV's sophisticated attack on the human immune system. HIV, the human immunodeficiency virus, mutates much faster than other pathogens. Within each infected patient, one virus can multiply by the billions. This prolific replication creates endless opportunity for genetic mutations, some of which can enable the virus to avoid detection and attack by the patient's immune system.

With so many variants of the virus rampantly accumulating—and spreading—among people, HIV researchers have been hard pressed to find an immunization strategy capable of producing antibodies against HIV that are capable of "broadly neutralizing" diverse viral strains.

Yet we know that such a "magic bullet" exists. In rare cases, people infected with HIV are able to produce broadly-neutralizing antibodies on their own. Therein lies a tantalizing possibility—that a much more extensively-reaching, protective version of such an antibody could be induced in uninfected individuals through preventative immunization.

Bridging a gap from lab models to reality

Achieving this goal requires HIV researchers to take a whole new approach at eliciting broadly neutralizing antibodies in the laboratory. Mice—the most commonly used animal model for immunological studies like HIV research— are much, much smaller than humans. As a result, mice have far fewer immune cells called B cells, which are the cellular factories responsible for assembling antibodies and directing the immune system's attack on pathogens like HIV.

Thus, until now, working with mouse models of HIV has only allowed researchers to replicate a tiny percentage of the possible HIV antibodies that human bodies are capable of producing. What's more, it has been a slow process, reliant on mice's reproductive cycles.

"Conventionally, it has required the time-consuming breeding of multiple generations of mice to generate humanized models for testing how to elicit highly-evolved, highly-mutated HIV antibodies," says Alt.

So, Alt and his team developed a nimbler vaccine test system that could speed up natural "evolution" of human antibodies in mice.

Turning evolution against HIV

First, they engineered mouse embryonic stem cells so that they would rapidly develop into mice containing humanized versions of the genetic

building blocks that B cells use to assemble antibodies. Then, partnering with collaborators at other institutions, the team immunized the mice with specially-designed HIV antigens, coaching their immune systems to produce increasingly varied antibodies. Some of these antibodies were eventually able to neutralize viral strains.

"Rather than go through generations of mouse breeding to make models, our approach allows us to quickly delete and replace genomic elements to create changes in B cells," Alt said in a Vector story about the advance. "Thus, we can rapidly re-program our mouse model with the intermediate antibody genes selected from the first successful immunizations, and expose them to new antigens. Over time, we hope this process will lead to a vaccine strategy that will elicit broadly neutralizing HIV antibodies."

It is a promising-enough strategy towards developing an HIV vaccine that the Gates Foundation is now investing in further enhancing Alt's mouse models. With the foundation's support, an essential piece is making the modified mice available to other major HIV research teams, further speeding the search for ways to induce broadly-neutralizing antibodies against HIV.

"The foundation is setting up ways to distribute our models and providing funds for investigators to use them and collaborate with us on collective next steps in this field of research," says Alt. "It's set up as a system that supports people who receive the model, insuring that they can do their part. A big team effort such as the Collaboration for AIDS Vaccine Discovery is the only way we will find a way to combat HIV—a research consortium like this is a great way to go after a disease."

Provided by Children's Hospital Boston