How High-Tech Computers Designed a Promising HIV Vaccine

A machine learning algorithm designed small sets of proteins that boasted the greatest potential to elicit a broad-based immune response.

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If only Darwin could see the high-tech version of his vision of evolution currently at work in the field of HIV vaccine research. Seeking to outfox a virus that evolves and mutates at a furious pace, researchers as Los Alamos National Laboratory (LANL) in Sante Fe, New Mexico, looked to a cutting-edge machine-learning algorithm to recapitulate HIV's evolutionary patterns in an effort to develop a promising vaccine candidate.

HIV vaccine research has been beset by numerous discouraging setbacks since the first late-stage trial of a candidate began two decades ago. Thus far, only one such trial has shown any success: a Thai study, published in 2009, in which the investigational vaccine reduced HIV risk by a modest 31%.

Now two major HIV vaccine trials are under way, and signs suggest that the candidates under investigation may reduce transmissions of the virus by at least 50%, which is generally considered the minimum efficacy needed to justify a global vaccine rollout.

One of those trials, a Phase IIb/III study known as HVTN 702, began in 2016 and is testing a retooled version of the Thai vaccine.

The other is the Phase IIb HVTN 705/HPX2008 trial, known as Imbokodo, after the Zulu word for "rock." The word refers to a South African proverb that pays tribute to women's strength and their central roles in communities.

Backed by Janssen, the National Institute of Allergy and Infectious Diseases (a division of the National Institutes of Health) and the Bill & Melinda Gates Foundation, the randomized, double-blind, placebo-controlled Imbokodo trial launched in November 2017 and is in the process of enrolling a planned 2,600 at-risk women 18 to 35 years old in various sub-Saharan African nations. The trial should complete its primary phase in November 2020 and will likely wrap up entirely in May 2022.

The Imbokodo vaccine candidate was designed in part through the computer-algorithm-based investigations of Bette Korber, PhD, a laboratory fellow and scientist in the theoretical biology and biophysics group at LANL.

Bette Korber of the Los Alamos National Laboratory Source: Los Alamos NationalSource: Los Alamos National Laboratory

The resulting candidate is based on what are known as mosaic immunogens, meaning the vaccine includes multiple components that have been designed by a computer to optimize their potential to prompt the body to develop a powerful immune response against a wide range of circulating global HIV strains.

A pair of earlier-stage studies of the Imbokodo vaccine, known as APPROACH and TRAVERSE, have given researchers good reason to hope that their vaccine will indeed reduce HIV risk to a substantial degree. In those trials, the vaccine has been associated with a broad spectrum of immune responses to HIV, including both antibodies and immune cells primed to target the virus, that thus far have persisted in the body for as long as a year.

The version of the vaccine that wound up prompting the best immune response in human participants of those earlier trials had previously boasted an impressive effect among nonhuman primates. This particular vaccine variant, which was ultimately advanced to the Imbokodo trial, reduced macaque monkeys' risk of SHIV, a simian version of HIV used for research purposes, by 94% per exposure to the virus and by 67% after six exposures.

Women in the Imbokodo trial are receiving four shots of a prime vaccine known as Ad26.Mos.HIV at the study's outset and at months three, six and 12 of the study. This shot includes a mosaic of various manufactured HIV proteins, or antigens, synthesized and selected thanks to Korber's research. These antigens are packaged in an engineered strain of the common-cold virus —one that doesn't make people get sick—called Ad26, which acts as a viral vector that delivers the mosaic antigens to the immune system. Ad26 was developed in the laboratory of Dan Barouch, MD, PhD, at Harvard Medical School's Center for Virology and Vaccine Reserach.

Dan Barouch speaks at the 2018 Conference on Retroviruses and Opportunistic Infections in Boston.Benjamin Ryan

Additionally, the participants receive a pair of booster shots at months six and 12 of the study. These injections include an aluminum phosphate adjuvant, which boosts immune responses to vaccines, as well as an HIV antigen—also selected by Korber's computational process—called gp140 that in its natural state is found on the surface of the virus.

It took a decade to settle on the mosaic of antigens included in the final vaccine undergoing testing in Imbokodo. Korber reports that early on, she and her colleagues struggled to get biologists on board with the notion that a computer could design viral proteins to serve as the basis of a viable vaccine candidate.

Perhaps, as it turns out, only an advanced computer program can match HIV's wily complexity. The virus mutates and evolves so rapidly in natural settings that a vast breadth of major strains is

circulating around the world, and every person's individual infection is genetically distinct. Even within one person's body, the population of virus varies genetically.

All this viral evolution makes designing a vaccine particularly challenging, because a vaccine that goes after one type of HIV may not be broad-based enough to prevent other viral strains.

"The extraordinary variability of HIV is a huge problem," says Korber.

Research has indicated that prompting a solid antibody response to a vaccine requires using as a component of a vaccine the HIV protein kown as Env, which is a highly variable part of the virus. In other vaccine design approaches, researchers have sought to develop vaccine candidates based on parts of the viral genome that are highly conserved, or common, across the global population of HIV. In addition to using Env, the Imbokodo vaccine also relies two proteins that are more conserved.

"You want an immune response that elicits immune cells that are able to recognize the vast majority of these variants if you're going to be able to protect against them," Korber says.

Here's where the computer savvy comes in. Los Alamos holds a publicly available database of more than 800,000 genetic sequences of HIV from around the globe. Relying on this resrouce, Korber's team fed many thousands of sequences of natural proteins into a computer programmed with a machine-learning algorithm that synthesized what is known as a recombination of those sequences.

Recombination occurs naturally during HIV infection when one virus has entered a cell and a second virus follows suit—a double-infection process that occurs despite the fact that an infected cell is supposed to block the entry of any new viruses. These two copies of HIV will then combine their genomes into a single new virus.

Korber's computer system recapitulates this recombination process thousands of times, continuously selecting for protein designs that provide better and better coverage of HIV's global diversity. The resulting genomes of the key viral proteins have written into their genetic code central commonalities shared by the thousands of types of HIV.

"They are natural sequences that look and feel like natural sequences that have been evolved in a computer under selection, following Darwin's ideas," Korber says.

Korber is keen to refute a common misconception that a massive supercomputer is required to conduct such calculations. During the Imbokodo vaccine development, a laptop could complete the recombination synthesis in about 24 hours. Los Alamos now has a faster program that can conduct such calculations in only a few seconds.

The Imbokodo vaccine candidate's association with both an immune-cell-based and antibody-based response to HIV is particularly promising because immune cells have a greater capacity to target parts of the virus less prone to viral-evolution-driven variation than those viral targets that

antibodies go after. This effect could improve the vaccine's ability to provide protection against different types of HIV.

Additionally, it is possible that if an individual who received the vaccine nevertheless contracted HIV, his or her immune cells would already be primed to combat such an infection. This might in turn reduce the infection's transmissibility. (Crucially, people who have contracted HIV very recently naturally tend to have a very high viral load, greatly increasing their risk of passing on the virus.) Such primed immune cells might also help the body better control the virus over the long term, potentially improving health outcomes.

"If it isn't a success, I know we'll learn from it," Korber says of the Imbokodo trial's vaccine candidate as she and other scientists wait for results to come in late next year. "But if it was successful enough to be useful, it would just be wonderful to have this to build on. I don't think it's going to be an end point. We'll just have to see what happens. It is promising in macaques, so that's encouraging."
