New wave of HIV vaccines: Promises that can be fulfilled or more pipe dreams?

In 1984, after researchers discovered that human immunodeficiency virus (HIV) was the causative agent for AIDS, Margaret Heckler, then U.S. Secretary of Health and Human Services, announced that a vaccine could be expected within two years to fight a disease that had proven to be one of the most devastating epidemics of the 20th century: AIDS. Significant successes around that time in vaccination programs, such as eradication of smallpox and the development of the polio vaccine, may have prompted Heckler to make that optimistic projection, but little did she know how foolishly bold it would prove to be.

Fast forward 31 years. While we know a lot more about the biology of the virus, the search for a vaccine has been frustratingly elusive. Researchers developed several candidates which showed efficacy in animal models but failed when they came to human clinical trials. The search has frustrated researchers so much that last week, Francoise Barre-Sinoussi, a French scientist and co-discoverer of the HIV for which she won a Nobel Prize, said in an interview with CNN that "a cure [for HIV] is an almost impossible mission".

But maybe not. A new class of HIV vaccines are being developed that could change the status quo. Called broadly neutralizing antibodies, these drugs have the potential, Nature writes, to "prevent, treat or even cure HIV", offering what some are calling a "new hope for HIV patients."

Is the new wave of HIV vaccines truly promising or yet another deceptive blip on the radar?

Checkered past

When infected by a virus, our immune system learns to recognize it by its characteristic proteins. However, over years of evolution the AIDS virus developed many ways to evade the immune system and conquer its host. Chief among these is its rapid rate of mutation by which it constantly changes the proteins on its surface, flummoxing the immune cells by constantly presenting a new face. Secondly, the virus targets the very same immune cells that are supposed to help clear it out of the body. Between its chameleon like property and its ability to break down the only mechanism in the body capable of fighting it, HIV has become a feared and ferocious virus.

Attempts at making an HIV vaccine thus far have been largely unsuccessful. Two major clinical trials (AIDSVAX and STEP) conducted between 2000 and 2010 aimed at either trying to induce the immune system to produce antibodies that could disable the virus or increasing the production of immune 'T cells' that were capable of killing the virus. The candidates chosen for the trials were considered extremely promising because they had been shown to prevent infection in animal models. The trials turned out to be a major disappointment as neither showed significant efficacy. A third trial conducted in Thailand that combined the AIDSVAX vaccine with another candidate showed limited success. The results however were marginal at best and attempts to improve its effectiveness are in progress.

New paths to explore and lessons to be learned

Around the same time as the disappointing results of the clinical trials were being dissected, researchers found that certain individuals who were infected managed to maintain very low levels of the virus in their blood for a long period of time, an unusual and unexpected occurrence. These patients, known as ‘elite controllers’ seemed to somehow naturally develop antibodies against HIV that were able to target multiple strains – so called ‘broadly neutralizing antibodies’ (bnAbs). It took a while for these bnAbs to develop however. This was thought to be a function of how the body develops new antibodies. Through a process of trial and error over several years, immune cells in the elite controllers had developed antibodies that recognized certain parts of the viral coat proteins that changed less frequently than the others.

By using elite controllers as a blueprint, researchers have begun to understand how B cells (the antibody producing cells in the body) produce bnAbs and the viral coat proteins that these antibodies target. The ultimate goal of this approach is to develop a vaccine that can elicit similar responses to the virus as the controllers.

The most promising result for bnAbs so far have occurred in a small human clinical trial reported in April. Researchers tested the effectiveness of an HIV antibody called 3BNC117 by injecting it into patients with HIV and found that it significantly reduced the amount of the virus in the patient’s blood. The results did come with the caveat that the drug used on two of the eight patients given the highest dose of the antibody lost 80 percent of its effectiveness within 28 days, indicating that the virus may have mutated to evade detection.

There are obviously many roadblocks to cross before broadly neturalizing antibodies might see store shelves. Methods to maintain the levels in the blood for a longer period of time need to be developed. While human clinical trials that employed transferring bnAbs showed promise, only a vaccine that can elicit a sustained response will be viable. It also cannot be the only method of treatment, for the bnAbs may not broad enough to recognize all the different variations of the virus and HIV itself may evolve to evade the antibodies. One approach to tackle this according to researchers is to use a combination of different antibodies to reduce the chances of resistance. And lastly, an ‘antibody only’ approach is unlikely to work as pointed out by Dr. Leo Stamatatos, a vaccine researcher at the Fred Hutchinson Cancer center in an article discussing the advances in bnAbs.

> We think now that broadly neutralizing antibodies will be a critical component of an effective vaccine, but I don’t think personally it will be the only one.

To that end several complementary approaches are already in the works, including stimulating the T cells that can kill the virus and improvements upon the RV144 candidate that showed limited efficacy in the Thai trials. Advances in technology and the accumulated knowledge about the underlying biiology of HIV and how it interacts with our body have taken us farther than we have ever gone before in this search.

Interestingly however, we seem to be in a similar position to when the AIDSVAX and STEP clinical trials were conducted: Lots of promise in animal models with limited or no evidence in human studies and news reports of a solution just around the corner. TIt is important to maintain perspective. Judging by the history

of AIDS vaccine development it seems prudent to take a cautious approach and view any headlines about ‘AIDS vaccine within reach’ or ‘breakthrough treatments’ with a heaping spoonful of salt. While we certainly seem to be a few steps ahead of where we were a decade ago, they are only baby steps.

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