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Scientists inching ever closer to HIV vaccine

By: Bradley Fikes | December 6, 2016

For decades, success has seemed to be in sight for a vaccine to stop the spread of HIV. And for decades, the success has proven to be an illusion.

Once again, new vaccine candidates are being readied for trial. And while researchers have learned to be cautious about predictions, an ever-deeper understanding of how HIV works has produced a solid body of science on how it might be thwarted.

In a fraction of those infected, powerful antibodies that neutralize a wide variety of HIV strains are produced. Unfortunately, these neutralizing antibodies are produced too late in the infection process to stop the disease. But if the immune system could be trained to make them in advance of infection, in theory HIV should be stopped in its tracks.

Scientists at San Diego biomedical institutions have been leaders in this intensive effort. And recently, they've discovered another important step in producing a effective vaccine, how to prime the immune system to make powerful antibodies that neutralize a broad range of HIV strains.

The levels of these broadly neutralizing antibodies correlates with the condition of certain cells found in immune tissues called germinal centers, say researchers led by Shane Crotty of the La Jolla Institute for Allergy & Immunology.

Germinal centers have been called the "black boxes" of the immune system. They are the home where antibody-making cells mature into potent pathogen-killing machines. But nobody knows just how this process happens. And because the immune system consists of so many components, finding out which parts are necessary to generating the broadly neutralizing antibodies is critical.

The discovery not only gives clues as to what is going on inside the machine, it also provides a means of checking whether a vaccine candidate is leading the immune system down the right path.

The researchers performed their work in rhesus monkeys, regarded as the best animal model for the human immune system.

The study was published Nov. 22 in the journal *Cell Reports*. It can be found at: j.mp/germinalcenter. Among the authors were other well-known names in HIV vaccine research, including Dennis R. Burton of The Scripps Research Institute, which hosts a major HIV vaccine research center. Burton and colleagues have collected broadly neutralizing antibodies for years, studying them to understand how they work.

"While some people do develop HIV broadly neutralizing antibodies it is too late to be helpful to them," Crotty said. "By 3 years postinfection the virus is far too ingrained — too many millions of integrated viral genomes — for the antibodies to help. This is a reason the amazing antibodies were missed for so many years, and only someone as persistent as Dennis Burton managed to find them."

Crotty has focused on the germinal center, leading a series of studies probing its function. In 2013, he published a study explaining the link between "helper" immune cells and the B cells that make neutralizing antibodies. A 2015 study described the mechanism that generates fully functional "helper" cells.

The researchers also solved a problem that until now had hampered closer examination of the germinal centers, the inability to see them change over time. While lymph nodes can be removed for biopsies, that can be done only once. But germinal centers must be repeatedly measured to correlate their internal state with production of neutralizing antibodies.

Innovative idea

The La Jolla Institute's Colin Havenar-Daughton, the study's first author, found that repeated samples of germinal centers could be taken by drawing out very small portions of fluid "aspirates" with fine needles. This method is often used by oncologists to assess the state of lymph nodes, where circulating cancer cells tend to accumulate.

The study provided an innovative way to tackle a previously intractable problem, said Marcella Flores, associate director of research at the American Foundation for AIDS Research, or amfAR,

"It's a great example of technologies coming in from outside the field of HIV," Flores said. "It's something that amFAR is really interested in. The study itself is great for the vaccine world."

While the ability of neutralizing antibodies to block HIV is important, amFAR would like a vaccine to produce other effects, such as prompting the immune system to kill already infected cells, Flores said.

"That's what would lead to a cure," she said. "While these (preventive vaccination) studies represent a huge step forward in the vaccine world, we still need more information on whether the processes they've identified would lead to a cure."

Curing HIV presents a particularly difficult challenge because the virus can hide out in a dormant form, inside the genome of the immune cells it infects. While inactive in the genome, it's beyond the immune system's reach. Only when infected cells begin producing more viruses does the immune system recognize the infection.

Some ingenious curative efforts are now being tested on HIV patients. Sangamo BioSciences of Richmond, Calif, is genetically altering immune cells of HIV patients so the cells can't be infected. The cells are taken from the patient, genetically modified and reinfused. The treatment is in Phase 2 trials.

A similar trial is now being carried out by Tucscon-based Calimmune, founded by three scientists; Nobel Laureate David Baltimore of Caltech; Irvin Chen of UC Los Angeles and Inder M. Verma of the Salk Institute for Biological Studies.

But in the long term, HIV prevention will be more effective and much less costly. And that's what Crotty and many other researchers are focusing on.

Blocking the virus

Vaccines against some viruses, such as smallpox or polio, can be prepared from relatively simple derivatives of the virus. However, HIV presents a much more difficult target for the immune system. It mutates extremely rapidly, and also presents decoy proteins that fool the immune system. HIV's vulnerable regions are hard to find.

To be effective, a vaccine must produce immunity in the vast majority of those who are vaccinated, known as "herd immunity." When immunity is that widespread, those who can't be vaccinated for some reason, such as pregnancy, are still protected from exposure to the pathogen.

Previous efforts to develop a safe and effective HIV vaccine, such as one led by The Immune Response Corp., a now-defunct Carlsbad biotech, failed to yield such a vaccine. That company's vaccine, Remune, yielded some modest signs the immune system was being stimulated, but didn't gain approval by the U.S. Food and Drug Administration.

Given HIV's elusive nature, effective HIV neutralizing antibodies must be highly specialized. In most people it takes the immune system three or more years to make them. By that time HIV is well established and if untreated, leads to AIDS.

Vaccine researchers aim to speed up this process by a series of immunizations that telescope the immune education process into several weeks. To do so, they need to

understand what is going on inside the immune system, to prepare the right ingredients to guide it along the right path.

To get access to the rhesus monkeys, Havenar-Daughton allied with Dr. Guido Silvestri and colleagues at the Yerkes National Primate Research Center. Using the needle biopsy method, they studied the germinal center response of 12 monkeys that had been immunized by an HIV protein that's to be tested for a vaccine.

The researchers discovered the correlation between the cellular response inside the germinal centers. Unexpectedly, they also found that the levels of all antibodies in the blood didn't correlate with production of neutralizing antibodies. That meant the strength of the pertinent immune response was only evident from actual inspection of the germinal center.

Of the 12 monkeys, nine produced neutralizing antibodies. A better response is needed for a vaccine, Havenar-Daughton said in a La Jolla Institute statement.

"It was a very good response but if you go into humans you want everybody making neutralizing antibodies and not just some people," he said. "We need to solve this problem."