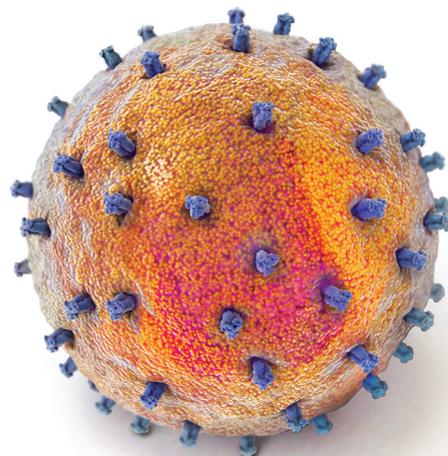


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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

Inching Closer to Neutralizing Antibody-based Vaccines

Recently published research studies showcase progress in the development of vaccine candidates designed to induce powerful antibodies against HIV. *By Kristen Jill Kresge*

Antibodies pack a powerful punch. These typically Y-shaped proteins are the reason most, if not all, licensed vaccines provide protection against disease (see *VAX* July 2014). So it is not surprising that researchers long ago set their sights on inducing them against HIV.

Researchers have been actively pursuing ways to design vaccine candidates that could induce broadly neutralizing antibodies (bNAbs) for decades with little success. Now, thanks to recent developments in stabilizing the virus and in understanding how antibodies develop during the course of natural HIV infection, researchers are inching closer to this goal. A trio of research studies published recently showcase promising first steps in developing vaccine candidates that are capable of effectively stimulating the immune system and launching it in the direction of being able to induce bNAbs against HIV.

There are still many obstacles to developing an effective bNAb-based HIV vaccine, but this latest research is inspiring optimism. John Mascola, director of the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), who was not involved directly in the most recent studies,

classifies this work as a “major advance.”

All hail antibodies

Antibodies work in many different ways. One mechanism of action is to bind to and inactivate viruses, such as HIV. Antibodies that can inactivate, or as scientists say neutralize, many different strains of HIV that are in circulation are referred to as broadly neutralizing antibodies, or bNAbs for short. While vaccine candidates developed previously could induce antibodies against HIV, none so far has induced bNAbs. Many researchers think that a vaccine that induces bNAbs against HIV will be the most effective way to protect against infection.

But at the same time, there is also great interest in other antibody activities. This includes efforts to build on the low level of protection induced by non-neutralizing antibodies in the [RV144 trial](#) in Thailand, which was the first and so far only vaccine regimen to show any efficacy in humans.

Over the past six years, researchers have made great advances in isolating new bNAbs. New techniques for fishing antibodies out of serum samples collected from HIV-infected individuals as well as improved means of ana-

lyzing these antibodies and how they bind to the virus are allowing researchers to characterize bNAbs at what in this field is nearly break-neck speed. After decades of working with just a handful of antibodies, researchers now have scores of more powerful and potent neutralizing antibodies to study. They also are gaining a better understanding of how these bNAbs naturally develop during HIV infection.

Despite the great success in isolating these powerful antibodies, they still are a rare occurrence. Researchers estimate that the immune systems of only 20% of HIV-infected individuals make such antibodies, and they take years to develop. These bNAbs have unique characteristics that allow them to neutralize HIV so well. Many of them have accumulated multiple changes or muta-

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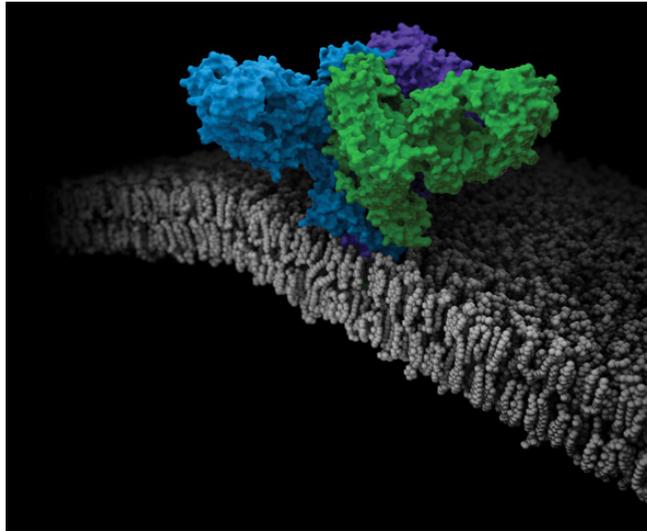
tions as a result of continuous exposure to the constantly mutating virus. Following infection, the virus and the immune response against it engage in a bit of a cat and mouse game. By the time antibodies against HIV develop, the virus mutates enough to escape this antibody response. This process of antibody development and virus escape continues for years until the antibodies mutate and mature enough to become broadly neutralizing. By this time, the bNABs do not help infected individuals control the virus. But administration of these antibodies to mice and monkeys is able to ward off infection with a virus similar to HIV, stoking hopes that if such antibodies could be induced by vaccination they would also protect humans against infection.

Why so hard?

There are many reasons that inducing antibodies that could neutralize the vast array of HIV variants in circulation is proving a difficult task. Chief among them is that the target of all antibodies against HIV is the notoriously unstable Envelope or Env protein that dots the surface of HIV (see image, this page). This protein spike, also referred to as the trimer, is so floppy and highly mutable that for years researchers were stymied in their efforts to recapitulate its structure in order to develop a vaccine candidate based on this protein.

This changed in 2013 when after almost two decades of failed attempts, John Moore, professor of microbiology and immunology at Weill Cornell Medical College, and colleagues reported successfully stabilizing an HIV Env protein designated BG505 SOSIP.664. This stabilized HIV Env protein was based on a naturally occurring virus iso-

lated from a six-week-old Kenyan infant who developed bNABs after approximately two years of infection. Just having in hand a protein that closely mimics the natural structure of HIV Env was a big accomplishment. "This represents more than 10 years of hard work and good virology," says Mascola.



The HIV Envelope (Env) protein actually consists of three identical parts that make up what is called the trimer (shown here in green, blue and purple). HIV uses the Env trimer to infect cells. Broadly neutralizing antibodies can bind to the Env trimer at various spots and interfere with the virus's ability to infect cells and eventually lead to destruction of the virus. Image created by Graham Johnson (UCSF; grahamj.com).

But the real test was to see if this protein would induce antibodies. Researchers from the University of Amsterdam and Weill Cornell Medical College recently published the results from vaccinating rabbits and monkeys with the BG505 SOSIP.664 protein. They also immunized animals with another stabilized Envelope trimer based on a virus isolated from an infected adult. The data indicate that these proteins induce antibodies, but these antibodies are not able to broadly neutralize a wide variety of viruses that are representative of those currently circulating

around the globe. These results are, however, what the study's authors call an "excellent starting point for iterative vaccine design."

Researchers are planning several modifications to improve upon these first attempts. One strategy is to immunize with a series of different stabilized HIV Env protein trimers either sequentially or as a cocktail. Another is to remove the portions of the Env proteins that are not the target of bNABs and may therefore just distract the immune system. "We are going to do all we can to refine their design and learn how to use them better," says Moore. "Our goals now are to devise ways to broaden the neutralizing antibody response. Only if we can succeed in doing this will we have a chance of coming up with a practical vaccine that might confer a meaningful degree of protection from infection."

Reverse engineering

Another approach to inducing bNABs against HIV that is gaining traction involves reverse engineering vaccine candidates. It works like this: researchers identify bNABs from HIV-infected individuals and then study precisely where on the virus these antibodies bind. They then use this information to work backwards and design a vaccine candidate based on this spot on the virus. The boon in antibody isolation over the past six years shows that there are multiple sites on HIV Env where bNABs bind, giving researchers many different targets to work with in designing vaccine candidates.

One class of bNABs that is widely studied targets the site on HIV that the virus uses to infect cells, known as the CD4 binding site. Researchers at the VRC identified the first antibody from this class, known as VRC01.

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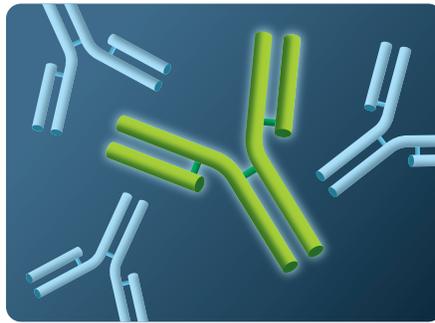
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Since then, VRC01-like bNAbs were identified in at least seven different HIV-infected donors.

VRC01, like many of the bNAbs recently identified, is no ordinary antibody. It and others in this class of antibodies have accrued many mutations in response to the feverish mutation of HIV. While not all of these mutations are necessary for these antibodies to neutralize the virus, many of them are. To encourage the immune system to generate such highly mutated and evolved antibodies, researchers are trying to use a step-wise approach to guide the development of VRC01-like antibodies.

They start by determining what the original version of the VRC01-like antibody most likely looked like before it became extensively mutated. Then they design a vaccine immunogen (the component of a vaccine candidate that triggers an immune response) that will hopefully induce this antibody. Finally, using a series of different immunogens administered sequentially, researchers attempt to guide the immune system to develop more and more mutated, and therefore more broadly neutralizing antibodies.

In a recently published paper, researchers from The Scripps Research Institute



An illustration of a Y-shaped antibody that can bind to and neutralize viruses, such as HIV.

(TSRI) in La Jolla, IAVI's Neutralizing Antibody Center, and the Ragon Institute showed they could successfully initiate the first step of this process in mice.

Joseph Jardine, a postdoctoral research fellow in Bill Schief's laboratory at TSRI, and colleagues engineered an immunogen designed to induce antibodies that are similar to the earliest, less mutated version of the VRC01 antibody. Mice immunized with a single injection of this immunogen developed antibodies with characteristics similar to that of the VRC01 class of antibodies, whereas the BG505 SOSIP.D664 protein did

not. By 42 days after immunization, many of the antibodies in the vaccinated mice had accrued mutations that resulted in more than a 1,000-times increase in their binding activity to HIV, a welcome result.

"We've initiated this process and we think that's a big step forward," says Jardine. "You knew it was a long shot when you started out. There were so many reasons it could fail. It's so cool that it worked out."

In a related study, researchers at The Rockefeller University collaborated with the TSRI researchers to test the same immunogen in a different mouse model. This study produced similar results.

Now researchers are plotting studies to test the second step in the sequential immunization strategy. They speculate that a series of at least four immunizations with different immunogens will be required to induce the type of broad neutralizing activity conferred by VRC01-like antibodies.

"These are important first steps toward cultivating broadly neutralizing antibodies against HIV in animal models of the disease and they suggest that clinical trials may soon be underway," says Mascola.

GLOBAL NEWS

IAS 2015: From Science to Progress

More than 6,000 participants from about 125 countries are expected to convene in Vancouver, Canada, from July 19-22 for the 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015). This bi-annual meeting comes at a critical moment in the fight against AIDS, according to Chris Beyrer, current president of the International AIDS Society (IAS) and a professor in the Department of Epidemiology at the Bloomberg School of Public Health at Johns Hopkins University. Studies of the optimal timing for the administration of antiretroviral treatment (ART) as well as recent discoveries related to virus-fighting proteins known as antibodies are ushering in a new chapter of HIV prevention and treatment.

"You put all these advances together and what you get is a scientific conversation," Beyrer says. "How do we realize the benefits that such research can provide?"

The upcoming IAS meeting will serve as a forum for discussing how to put this new knowledge into action, says Mark Harrington, executive director of the New York-based Treatment Action Group. The meeting's location is also significant, he said. Vancouver was where the bellwether 1996 IAS meeting occurred. That meeting ushered in the use of triple combination antiretroviral therapy, forever changing the way HIV treatment is administered.

But there is still much work to be done. "We need to not lose our commitment to research for a cure and a vaccine to finally wipe HIV off the planet," says Harrington.

Vaccine and cure research will be the focus of several pre-conference symposia and conference sessions. Prior to the start of the conference, IAS is hosting the fourth annual Towards an HIV Cure Symposium. A satellite session titled, "What's Next for HIV Vaccines: From design to efficacy testing," will take place on the opening day of

IAS 2015. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, will also speak about vaccine research at a session titled, "Progress and challenges in HIV prevention: Vaccine and non-vaccine approaches."

Attendees at IAS 2015 can also expect to hear the full results of the START (Strategic Timing of Antiretroviral Treatment) trial, Beyrer says. Early reports are that the study conclusively showed that HIV-infected volunteers receiving ART immediately were at a considerably lower risk of developing AIDS or of suffering from other serious illnesses or death. Together with data from previous studies showing that ART reduces the risk of HIV transmission to uninfected sexual partners, these findings point to the need to revisit treatment guidelines, Beyrer says. — *Kitta MacPherson*



IAS 2015
vancouver, canada
8th IAS Conference on HIV Pathogenesis,
Treatment & Prevention 19-22 July 2015

Understanding the Viral Reservoir

Why is curing HIV such a daunting task? *By Michael Dumiak*

Only one person has ever been cured of HIV.

This person, Timothy Brown, also known as the “Berlin patient,” did not reach this point easily. Brown received two stem cell transplants from donors with a genetic anomaly that makes their cells resistant to HIV infection in addition to multiple rounds of cancer treatments aimed to cure him of leukemia. This hardly represents a viable strategy for curing HIV.

In fact, researchers are currently lowering their expectations for the sort of HIV cure that might be feasible. Rather than a traditional cure, which would require every bit of HIV be flushed out of the body, researchers are focusing now on what is more akin to

a long-term remission that would enable HIV-infected individuals to go for some extended period of time without requiring the continuous anti-retroviral therapy (ART), which so effectively controls HIV infection.

One of the biggest obstacles to an HIV cure and the reason HIV persists in the body even during therapy is something called the viral reservoir. This is the term researchers use to describe the pool of long-lived resting cells in the body that harbor HIV. If at any time ART is interrupted, these cells can awaken and begin actively producing virus.

Researchers do not know exactly how the viral reservoir is formed but assume that it likely begins, at least in part, soon after HIV enters the body and begins infecting immune cells known as CD4⁺ T cells. These immune cells are the preferred targets of HIV. Some CD4⁺ T cells may become infected by HIV just as they are about to transition from an active state to a resting or latent state in the body. Once

latent, these cells do not actively replicate or produce copies of HIV. As a result they are invisible to the immune system, and impervious to the effects of ART.

As part of current efforts to cure HIV, researchers are trying to better understand how the viral reservoir is established, exactly what types of cells constitute the reservoir, where these cells are in the body, and how best to awaken and decimate these cells.

A mysterious opponent

While researchers don't fully understand how the reservoir of latent HIV-infected cells is established, they do know it happens with startling speed. Studies in monkeys indicate the viral reservoir is established within days of exposure to the monkey equivalent of HIV. The case of the “Mississippi baby” suggests the viral reservoir may also be established quickly in humans. In 2010 a baby born to an HIV-infected mother received ART beginning just 30 hours after birth, even before medical staff had confirmed the baby's HIV infection status. After a month, researchers could not detect any HIV in the infant and therefore stopped ART. After two years the child remained HIV-free, firing hopes that a cure was achieved. But last summer the child's virus rebounded and treatment was resumed. This case suggests that even starting treatment within the first two days was not enough to prevent establishment of the viral reservoir.

Mapping the reservoir

Researchers widely agree that CD4⁺ T cells are the basis of the viral reservoir. But there are also other types of long-lived cells that may harbor HIV and researchers are now trying to determine where these viral hideouts may be.

It is possible the reservoir is spread throughout tissues, organs, and fluids, including in the lymph nodes, heart, lungs, spleen, brain, gut, or even within bones and the spinal cord. Researchers currently

have few options, none of them very reliable or comprehensive, for how to thoroughly measure the reservoir or determine exactly where it is. They are also hindered by the difficulty in collecting tissue samples. Being able to map out the reservoir and measure it would be useful to researchers trying to test ways to reduce or even eliminate it.

Overall, the viral reservoir may be relatively small: perhaps fewer than 10 million cells in an infected person. But in this case size may not matter. Scientists can grow enough virus from one single latently infected cell within two weeks to be able to detect HIV using standard tests. A sterilizing cure for HIV may therefore require eliminating every single cell of the viral reservoir, something researchers say is incredibly daunting.

Draining the reservoir

The ultimate goal of understanding the viral reservoir is finding ways to reduce or ultimately eliminate it. One strategy for doing so is called “shock and kill” or “kick and kill.” The idea is to use some agent—perhaps an anti-cancer compound or a genetically altered stem cell—to wake up latent HIV-infected cells and then kill them. Some kill strategies include using ART in combination with therapeutic vaccines or by directly administering anti-HIV proteins, known as broadly neutralizing antibodies, that are currently a crux of preventive vaccine research (see *Spotlight*, this issue).

Several strategies for draining the viral reservoir are under investigation and others will soon be tested in clinical trials. But because there is no reliable way to measure the extent of the reservoir, the only way to currently tell if these strategies are effective is to interrupt ART and see what happens. ■

Michael Dumiak reports on global science, technology, and public health and is based in Berlin.

