

AIDS Vaccine Research and Development: The Role of Broadly Neutralizing Antibodies

What is a vaccine?

A preventive vaccine is a substance introduced into the human body that teaches the immune system to detect and destroy a pathogen—which is a particular virus, bacterium or parasite that causes a preventable disease. All vaccines contain some harmless form or part of the pathogen they target. They exert their effects through the adaptive immune response, an arm of the immune system that learns to recognize and neutralize specific pathogens (as opposed to pathogens in general).

What is an antibody?

Antibodies are infection-fighting protein molecules that tag, neutralize and help destroy toxins and invading pathogens. They are secreted by immune cells known as B lymphocytes (a kind of white blood cell) in response to stimulation by antigens, which are molecules found on the targeted pathogens. Each antibody binds only to the specific antigen that stimulated its production. More specifically, it homes in on an epitope, a patch of the antigen characterized by a relatively unique shape or surface. A neutralizing antibody against HIV latches onto the virus's epitope and stops the virus from infecting its target cell—which is the CD4+ T lymphocyte, a central player in the adaptive immune response.

What is an immunogen?

An immunogen is a substance—an organism or an antigen—that consistently provokes an immune response. It is the active ingredient of a vaccine, the component that teaches the immune system how to detect and target the pathogen against which the vaccine is devised. Immunogens employed in vaccines might be a dead pathogen of interest, a pathogen that has been rendered harmless, molecules derived from that pathogen, or even isolated epitopes from antigens that are known to be responsible for eliciting antibodies of interest.

Why is it so hard to make a vaccine against HIV?

There are three major reasons HIV has proved such a formidable foe to vaccine designers and immune systems alike. First, it is by far the most mutable virus scientists have ever encountered. A number of different subtypes of the virus, known as clades, circulate in different regions of the world. Within those clades there is considerable variability, and, beyond that, the virus mutates furiously within the people it has infected. In fact, you will find more genetic variation in the HIV isolated from a single person who has been infected for a few years than you are likely to find globally in the dominant strain of influenza during flu season. As a consequence, researchers have not yet found a single, unchanging part of HIV that when used as an immunogen might teach the immune system to recognize and neutralize its countless naturally occurring variants. Second, because no one is known to have cleared an HIV infection, we do not know which elements of the immune response must be engaged to control the virus—and thus are uncertain how to replicate such responses. Finally, the immune system has a very narrow window of opportunity in which to neutralize HIV before the virus establishes a lifelong infection.

What is a broadly neutralizing antibody (bNAb)?

A bNAb is an antibody capable of blocking the ability of viruses from a number of types of HIV from infecting their target cells. Like other antibodies, they are produced by white blood cells known as B lymphocytes. Only a minority of people who are infected with HIV produce bNAbs.

Although HIV is a wildly mutable virus, certain parts of it are relatively resistant to change. These parts, for one reason or another, are essential to the virus's ability to infect the CD4+ T lymphocyte and multiply. In general, these elements of HIV are what bNAbs target.

Only a handful of such antibodies have so far been isolated from HIV-positive people, and all of them until now were derived from individuals infected with the subtype of the virus that circulates primarily in the Americas, Europe and Australia. Researchers at the International AIDS Vaccine Initiative (IAVI) and The Scripps Research Institute, along with other partners, have been collaborating with a large network of clinical research centers around the world to find more bNAbs, with a special emphasis on varieties capable of neutralizing subtypes of HIV that predominate in developing countries. This work has resulted in the discovery and characterization of two novel bNAbs, the first to come from an HIV type that predominates in the developing world, where an AIDS vaccine is needed most.

Why are broadly neutralizing antibodies (bNAbs) important to the AIDS vaccine effort?

bNAbs provide very valuable clues to effective immunogen design. Careful study of their mechanisms of action reveals vulnerabilities that are shared by many different types of HIV. Most importantly, this research exposes the epitopes on HIV—those particular shapes recognized by bNAbs—that, if reproduced in a lab and delivered in a vaccine, might elicit similar antibodies in those who are vaccinated, conferring immunity to multiple types of HIV. The two recently identified bNAbs reveal a new target on HIV that is potentially a more accessible site on which to focus vaccine design efforts than the targets provided by previously identified bNAbs.

What do we know about existing bNAbs?

Researchers at labs around the world have charted, in atomic detail, the structure of a number of these antibodies and pieced together a pretty clear picture of how each latches on to its target epitope. Not surprisingly, given the difficulty of neutralizing HIV, the antibodies studied in detail so far display unique structural and mechanistic characteristics that complicate attempts to elicit them through a vaccine.

How is this information being used in AIDS vaccine research?

Researchers are using information generated from the close study of existing bNAbs to inform the design of what they hope will be a new class of AIDS vaccines. For example, members of the Neutralizing Antibody Consortium (NAC)—which was launched in 2002 by the International AIDS Vaccine Initiative and is directed by Dennis Burton, professor of immunology and microbial science at The Scripps Research Institute—are applying powerful computational and protein engineering techniques to re-create the epitopes bNAbs latch onto and use them as immunogens for what might be called prototype HIV vaccine candidates. This work is still in its earliest stages, but when the researchers do construct an immunogen that elicits the desired antibody response in animal studies, it will be put through the steps required to turn it into a candidate vaccine for human trials.

IAVI, The Scripps Research Institute, Theraclone Sciences and Monogram Biosciences have just announced that they have found two new broadly neutralizing antibodies (bnAbs). What distinguishes them?

The two newly discovered bnAbs, called PG9 and PG16, are the first to have been identified in more than a decade and are the first to have been isolated from donors in developing countries, where the majority of new HIV infections occur. The bnAbs previously identified and studied by researchers in the NAC have all come from people infected with clade B HIV, which predominates in the Americas, Europe and Australia. Further, the newly isolated bnAbs neutralize a wider range of HIV subtypes than all but one of the existing bnAbs, and at low concentrations appear to outperform that antibody as well. They also seem to be far more potent than any of the previously isolated bnAbs.

What is the significance of these findings?

These antibodies are the first new bnAbs to have been isolated in more than a decade. They target a surface on the HIV spike, which the virus uses to infect cells, that none of the previously identified bnAbs targeted. This reveals a new and relatively unchanging spot on the highly mutable virus that vaccine designers may be able to exploit to generate immunogens (the active ingredients of vaccines). The breadth of neutralization of the new bnAbs makes them ideal candidates for study by AIDS vaccine designers, who must develop vaccines that protect people from subtypes of HIV circulating in developing countries if they hope to have a significant impact on the AIDS pandemic. The notable potency of these antibodies also holds promise: If they can be elicited via vaccination, they will not, in theory, have to be produced at very high levels in people to induce protection from HIV.

How will this discovery be exploited to support the design and development of novel vaccine candidates?

Like the previously discovered bnAbs, these new antibodies will now be closely studied by NAC researchers, who will work out their molecular structure and the precise mechanism by which they bind to their targets on the HIV spike. With this information in hand, they will begin trying to design novel immunogens to elicit these antibodies in all people. If they succeed, the immunogens will be put through the steps of preclinical development to produce an industrially viable vaccine candidate for further development. Similar efforts—albeit in the earliest of stages—are already underway within the NAC using the structural information derived from studies on previously discovered antibodies.

Will more bnAbs be found?

A number of collaborative efforts—including those of the NAC, the U.S. National Institutes of Health and the Collaboration for AIDS Vaccine Discovery—are currently engaged in a global hunt for more such antibodies. There is no doubt that more will be found and a fair chance that one or more of them will expose an Achilles heel on HIV that can be exploited by vaccine designers. Better yet, because these projects are global in scope they will yield antibodies that neutralize the types of HIV that predominate in developing countries, which is where 95% of new infections occur. All bnAbs identified until now have been derived from people infected with versions of HIV primarily found in Australia, the U.S. and Europe.