Progress on the Path Toward an AIDS Vaccine

Since it was first identified as the cause of AIDS in 1983, HIV has taken nearly 30 million lives. An estimated 34 million people are living with HIV, and each day an additional 7,000 become infected with the virus. Current responses to the pandemic have proved unequal to the challenge posed by HIV: For every person who gains access to antiretroviral drugs today, two are newly infected by the virus.

The world needs safe, effective and affordable preventive AIDS vaccines. But making such vaccines has proved extremely difficult. HIV is the most difficult foe vaccinologists have taken on. Not only has it developed multiple mechanisms to avoid detection and elimination by the body's immune response, but many different subtypes of the virus, known as clades, circulate in different regions of the world. Within those clades there is considerable variability. So far, researchers have not been able to design a vaccine capable of protecting people from all the variants.

Despite these challenges, researchers have recently made encouraging progress toward an HIV vaccine.

PROOF OF CONCEPT

A clinical trial completed in Thailand in 2009 provided the first demonstration in humans that a vaccine can prevent HIV infection. Two AIDS vaccine candidates, given a few months apart in a so-called prime-boost combination, were found to be about 30% effective at preventing infection with HIV. This result, while too modest to support regulatory approval for the vaccine regimen, has generated considerable excitement within the research field.

Researchers around the world have been working collaboratively to extract as much information as possible from the Thai trial data to inform future AIDS vaccine development. One analysis of this data indicated that two particular immune responses were significantly correlated with the HIV infection rate in vaccine recipients. Whether these immune responses are essential for achieving a protective effect with this or other HIV vaccine candidates needs to be confirmed in further studies. Two additional efficacy trials based on this vaccine candidate are also being planned in Thailand and South Africa - the latter study will test the ability of the candidate to recognize a different sub-type of HIV.

TESTING NOVEL VACCINE CANDIDATES

To date, some 30 AIDS vaccine clinical trials are ongoing, predominantly in early stages (Phases I and II). The HIV Vaccine Trials Network (HVTN) is currently testing one vaccine concept in a Phase Ilb efficacy trial, combining two vaccine candidates (DNA and adenovirus serotype 5-based). Results from this trial are expected in 2013. The International AIDS Vaccine Initiative (IAVI) and partners are currently testing two new experimental vaccine combinations. The first, a Phase I clinical trial conducted in the US, Kenya, Rwanda and South Africa, tests a prime-boost combination of two vaccine candidates based on vectors made from adenovirus serotypes 26 and 35. The second Phase



I trial, conducted in Kenya, Uganda and Zambia, tests the Ad35-based vaccine candidate in combination with a proteinbased vaccine candidate. Results from both studies are anticipated in 2012.

For an overview of ongoing AIDS vaccine clinical trials visit *http://www.iavireport. org/trials-db/Pages/default.aspx*.

A SPOTLIGHT ON BROADLY NEUTRALIZING ANTIBODIES

Most licensed vaccines are thought to work by eliciting neutralizing antibodies, which block a pathogen from successfully infecting cells. To prevent HIV infection, an AIDS vaccine would need to elicit antibodies that neutralize a large number of HIV variants. Researchers have long known that humans can make such antibodies. Until recently, only four antibodies regarded as



broadly neutralizing had been discovered and extensively studied by researchers. These antibodies, although broadly neutralizing, are limited in their potency.

Over the last two years researchers have made significant advances in this field of research, identifying more than 20 new broadly neutralizing antibodies, which have greater potency than those previously known. In September 2009, researchers at and affiliated with IAVI reported the isolation and characterization of a pair of novel broadly neutralizing antibodies, the first to be isolated from an individual in the developing world. These antibodies were found to be capable of targeting a remarkably wide spectrum of HIV variants. This discovery was closely followed by the isolation of a set of potent and broadly neutralizing antibodies by the Vaccine Research Center (VRC) of the US National Institutes of Health. Importantly, it was found that the combination of specific antibodies could neutralize 99% of all circulating variants of HIV.

Most recently, researchers at and affiliated with IAVI described the discovery of 17 additional antibodies, some of which have even higher potency than previously discovered antibodies. The more potent an antibody is, the less of it the immune system needs to produce to provide protection. Meanwhile, a team of researchers led by The Rockefeller University developed a novel approach and isolated a new crop of broadly neutralizing antibodies that target the CD4 binding site on HIV, the site where the virus engages the CD4 receptor on T cells to initiate its infection.

Additional advances have been made in identifying the structures of these antibodies and how they are produced by the immune system. These discoveries have aided researchers in identifying new targets for vaccine design, understanding where and how these antibodies interact with HIV, and how they are able to block the virus from infecting cells. A collaboration led by the VRC recently published a study mapping the way in which broadly neutralizing antibodies evolve. Collectively, these discoveries are providing essential clues on how to design and evaluate vaccine candidates that can elicit such antibodies.

Researchers have now begun to tackle the development of an "immunogen" the active ingredient in vaccines—that when presented to the immune system leads to the development of broadly neutralizing antibodies.

REPLICATING SUCCESSES

In addition to trying to improve the quality of the immunogens used in candidate vaccines, many researchers are also attempting to develop better genetic vehicles-or vectors-in which they are delivered. One approach aims to create vectors that are safe, yet capable of replicating like any naturally occurring virus. Researchers have removed the replication capability from most vectors being tested in HIV vaccine trials today. Yet vectors capable of replication could provoke more effective immune responses against HIV than have so far been observed. This idea has found a measure of support in a study on nonhuman primates.

Simian immunodeficiency virus (SIV) is closely related to HIV and causes an AIDS-like disease in non-human primates. The study of this virus provides researchers with insights into HIV infection and its prevention. In a study conducted by IAVI's partner, Oregon Health and Science University, non-human primates were given an experimental vaccine based on a novel replicating viral vector bearing immunogens derived from SIV. The candidate was designed to control, rather than prevent, infection. When the non-human primates were exposed to SIV, they went on to develop SIV infection. However, more than half of the vaccinated monkeys suppressed the virus so effectively that over time it could not be detected in their blood even by the most sensitive of tests. Importantly, the vast majority of these animals have maintained control over the virus for more than a year, gradually losing any signs that they had ever been infected.

Researchers, including those at IAVI, are currently building on these results by generating and testing several vectors that share the capacity to replicate, and so mimic a natural infection. Vaccine candidates based on these vectors could potentially improve the immune responses they generate and more effectively block or control infection compared with vaccine candidates that use non-replicating vectors.

SUSTAINING THE EFFORT

As illustrated by the scientific advances of recent years, the longterm investments that have been made in HIV vaccine development are showing distinct promise today. This hard-won momentum must be sustained. In the long run, continued progress in the field will depend on existing and novel funding mechanisms for AIDS vaccine research and development. It will also require the continued commitment and active support of governments, researchers, civil society and the communities in which the research is conducted.



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