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Spotlight

Researchers STEP up to the challenge

Questions linger, but so does determination, at the AIDS Vaccine 2008 conference

This year's AIDS Vaccine conference, which was held in Cape Town, South Africa, from October 13-16, was momentous on both political and scientific fronts. It was the first time the annual conference was held in an African country and Lynn Morris, conference chair and head of the AIDS unit at the National Institute for Communicable Diseases in Johannesburg, kicked off the conference by commenting on the particular significance of it being held in South Africa. "Nowhere else is the need for a vaccine greater than it is here," she said, adding that this conference sent an important signal that "we're not giving up."

Even more politically significant were the remarks made by the newly appointed South African Minister of Health, Barbara Hogan. After just two weeks on the job, Hogan made one of her first public addresses to the nearly 1,000 conference delegates. "We know that HIV causes AIDS," she said, immediately making her positions clear. "The science of HIV and AIDS is one of the most researched subjects in the medical field." Hogan also praised the conference organizers for holding the meeting in South Africa. "The timing of this conference coincides with a renewed interest in HIV prevention in this country. To the South African government and its people, there can't be any more important meeting to be held at this time." She called for evidence-based public health education as well as the development of evidence-based HIV prevention tools, which she said were critical to changing the course of the epidemic, and confirmed South Africa's commitment to conducting clinical trials of vaccines. Hogan's comments stood in stark contrast to those of her predecessor and were lauded by subsequent speakers.

On the scientific front, this year's meeting was momentous because it was the first to be held following the unexpected failure of Merck's adenovirus serotype 5 (Ad5) vector-based vaccine candidate (MRKAd5) in the STEP trial last fall, just after the 2007 conference. Since then the landscape of the AIDS vaccine field has changed dramatically. "The whole meeting has been held in the fallout of the STEP trial," said Edward Rybicki, a professor of microbiology at the University of Cape Town. This year's conference provided an opportunity for researchers, clinical trial investigators, and advocates to get the latest data from the STEP trial, as well as from Phambili—the second Phase IIb test-of-concept trial with MRKAd5 that is being conducted in South Africa. Researchers also debated some of the lingering questions about the potential for T-cell vaccine candidates, following the failure of MRKAd5.

Emerging Data

One of the key points of interest at the conference was, of course, the data emerging from the STEP trial. Since the results were first made public last September, they have practically become household news, at least in some circles. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health (NIH), said during his keynote lecture, "even the gardeners at the NIH know the three [key] bullets of the STEP study."

Julie McElrath, director of the Vaccine and Infectious Disease Institute at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, outlined progress in analyzing the data from the STEP trial in a plenary talk. She first noted that only 31% of vaccinees in the STEP trial had HIV-specific cellular immune responses, including $CD4^+$ and $CD8^+$ T cells, following three vaccinations with MRKAd5 (see *VAX* July 2008 *Special Issue, Understanding the Immune System and AIDS Vaccine Strategies)*. In a talk during the opening session of the conference, Stanley Plotkin, executive advisor to the CEO of Sanofi Pasteur, said such data suggested to him that the candidate's failure could be due to the lack of immune responses it induced. "The responses were inadequate," he said.

In fact, when McElrath and colleagues compared the T-cell responses induced by MRKAd5 to those observed in a group of long-term nonprogressors (LTNPs)—individuals infected with HIV who are able to control the virus or disease progression for an extended period of time without the aid of antiretroviral therapy—they found that average quantity of vaccine-induced $CD8^+$ T-cell responses in STEP trial volunteers were 43% lower than the average in

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HIV-infected LTNPs. "If we're trying to mimic the responses in these individuals, we're not there," said McElrath.

One of the troubling observations in the STEP trial was that certain sub-groups of vaccinated volunteers appeared to be at an increased risk of becoming HIV infected if they were exposed to the virus naturally—volunteers in vaccine trials are never purposely exposed to HIV. The volunteers at greatest risk were uncircumcised men, who also had pre-existing immunity to Ad5—a commonly circulating type of the cold virus that was used in MRKAd5 as a vector to shuttle non-infectious fragments of HIV into the body in the hope of triggering an immune response against HIV (see *VAX* September 2004 *Primer* on *Understanding Viral Vectors* and *VAX* September 2007 *Special Report*). Individuals previously exposed to this cold virus, which is prevalent in many areas of the world, typically harbor Ad5-specific neutralizing antibodies and in the STEP trial, individuals with higher levels of Ad5 antibodies prior to vaccination were more likely to become HIV infected.

So far, researchers have been unable to explain this observation, but in the meantime they are still looking for any effect MRKAd5 may have had on HIV disease progression in vaccinated volunteers. Holly Janes, an assistant member of the biostatistics program at FHCRC, presented data in the late-breaker session on a sub-group of male volunteers from the STEP trial who became HIV infected, despite vaccination, through natural exposure to the virus. In the group Janes analyzed, 33 individuals had received inactive placebo and 40 had received MRKAd5. Of these volunteers, 25 have already initiated antiretroviral therapy to treat their HIV infection. Janes reported that there was no significant difference between the median viral load—a measure of the quantity of HIV circulating in blood—between the vaccine and placebo recipients she analyzed, prior to their starting therapy. And on average, individuals in both groups started treatment around the same time. The $CD4^+$ T-cell counts, a marker of the health of the immune system, were also similar between these vaccine and placebo recipients prior to treatment, allowing Janes to conclude that there was no evidence to suggest that the vaccine had worsened HIV disease progression.

While the reasons for MRKAd5's failure are still unknown, and may never be completely clear, McElrath said investigators affiliated with the STEP trial have made further progress in defining the levels of immune responses that may be necessary for a vaccine candidate that induces cellular immunity. "There is much to be learned [from the STEP trial]," said Fauci, "and there are investigators pursuing just that."

Phambili data

Glenda Gray, executive director of the Perinatal HIV Research Unit in Soweto, South Africa, presented data collected so far from the Phambili trial. When immunizations in this trial were stopped last September, 801 volunteers had been enrolled, half of them women. While the STEP trial volunteers were primarily men who have sex with men, one goal of the Phambili trial was to enroll at least 50% women in order to evaluate the efficacy of the candidate against primarily heterosexual HIV transmission.

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>
> **Barbara Hogan**

Of the 400 volunteers in the vaccine group when immunizations were ceased, 66% had received two vaccinations and 7% had received all three. Gray reported that so far there have been 29 HIV infections, due to natural exposure to the virus, which have occurred among the 801 volunteers in Phambili. Of these infections, 17 were in vaccine recipients and 12 were in volunteers who received placebo.

Similarly to the STEP trial, most of the HIV infections that have occurred among participants in the Phambili trial were in volunteers with pre-existing antibody immunity to the Ad5 vector. In the Phambili trial, 16 of the 17 infections in the vaccine group and 9 of the 12 infections in the placebo group occurred in individuals with high Ad5 antibody levels.

Another risk factor associated with an increased risk of HIV acquisition among STEP trial volunteers was being uncircumcised, and of the seven HIV infections that have occurred among male volunteers in the Phambili trial, six were in uncircumcised men—four in volunteers that were in the vaccine group and two in placebo recipients.

Gray noted that the decision to tell the volunteers in the Phambili trial whether they had received vaccine or placebo—a process known as unblinding—has had a significant impact on the study. Since the study was unblinded a year ago, no new HIV infections have occurred among vaccinated volunteers. At the time of unblinding, volunteers who received MRKAd5 were counseled about a possible increased susceptibility to HIV infection due to the vaccine candidate. Because unblinding has clearly affected the data from the Phambili trial, Gray declined to make any comparisons between the Phambili trial and the results of the STEP trial.

Debating future efficacy trials

This year's conference also featured organized debate sessions at which pairs of researchers faced off over central questions currently dominating discussion in the AIDS vaccine field. One of these focused on whether additional candidates that induce only cell-mediated immunity and not antibody responses should be advanced into efficacy trials, given the failure of MRKAd5. In this session Gary Nabel, director of the Vaccine Research Center (VRC) at NIAID, and David Watkins, a professor at the University of Wisconsin-Madison, squared off against Dennis Burton, a professor of immunology at The Scripps Research Institute in California and scientific director of the recently-established HIV Neutralizing Antibody Center (see *Global News*, this issue).

This debate was originally scheduled when Fauci was still considering whether or not NIAID would fund a Phase IIb test-of-concept trial of a prime-boost regimen—a DNA vaccine candidate followed by an Ad5 candidate similar to MRKAd5—developed by researchers at the VRC. This trial was initially postponed after the STEP trial results were released, and then in July

Fauci rejected the proposed Phase IIb trial design, known as PAVE 100 (see *VAX* July 2008 *Spotlight* article, *AIDS 2008: A changing landscape for vaccine research*). NIAID is still considering conducting a smaller trial, what Steven Self, director of statistical and data management at the HIV Vaccine Trials Network, called the "redesign of the redesign of PAVE."

The protocol for a smaller trial, which is still under development, would only evaluate the ability of the candidates to lower viral load in individuals who become HIV infected despite vaccination.

But Nabel argued that efficacy trials of T-cell vaccines should continue and that these trials should be "sufficiently large" to be able to address whether these candidates can prevent HIV infection or lower viral load. Burton disagreed. He said there are "too many uncertainties at this time" to justify large-scale trials of cellular-immunity candidates. Instead, he voiced support for smaller studies known as screening-test-of-concept trials that involve fewer volunteers and only look at a candidate's ability to lower viral load. *—Kristen Kresge*

Global News

New neutralizing antibody research center established

A new research center, dedicated to developing AIDS vaccine candidates that can elicit broadly neutralizing antibodies against HIV, was established recently by The Scripps Research Institute and IAVI. The new HIV Neutralizing Antibody Center will be housed at Scripps in California, and was established with an investment of US$30 million from IAVI, extending the existing collaboration between the two institutions. The center will bring together researchers from diverse fields to work on solving what is arguably the single biggest biological obstacle blocking the discovery of a preventive AIDS vaccine—identifying how to induce neutralizing antibodies against HIV through vaccination. These Y-shaped molecules latch on to HIV and deactivate it, thereby preventing the virus from infecting critical cells of the immune system (see *VAX* July 2008 *Special Issue*, *Understanding the Immune System and AIDS Vaccine Strategies*).

None of the AIDS vaccine candidates or approaches tested so far in clinical trials has induced neutralizing antibodies against HIV, yet they are thought to play a critical role in many, if not all, of the currently licensed vaccines against other viruses and bacteria, and are believed to be critical to the development of an AIDS vaccine that could effectively block transmission of the virus. "We are excited and hopeful that this collaboration will help to bring us closer to developing a vaccine that will end the AIDS pandemic," says Seth Berkley, president and chief executive officer of IAVI.

Researchers at the new HIV Neutralizing Antibody Center will work to identify neutralizing antibodies from HIV-infected individuals and then will try to identify which immunogens—noninfectious pieces of the virus—could induce these antibodies. Scientists affiliated with the Neutralizing Antibody Consortium (NAC), an international consortium of researchers established by IAVI in 2002, will collaborate with researchers at the HIV Neutralizing Antibody Center, as well as with scientists in IAVI's own research and development program.

Dennis Burton, an immunology professor at The Scripps Research Institute and the scientific director of the HIV Neutralizing Antibody Center, says researchers will be venturing into "uncharted waters" that hopefully will yield a greater level of understanding about the mechanisms that enable vaccines to shield people from infection.

"Having the HIV Neutralizing Antibody Center will be a terrific help to the field," says Barton Haynes, director of the Duke Human Vaccine Institute and the Center for HIV/AIDS Vaccine Immunology at Duke University. "We shouldn't give up on this problem and the funding of this center is a signal of renewed commitment." *—Regina McEnery*

Nobel Prize awarded for discovery of HIV

This year's Nobel Prize in Physiology or Medicine was awarded to French researchers Françoise Barré-Sinoussi and Luc Montagnier for the discovery of HIV, as well as German researcher Harald zur Hausen for the discovery of human papilloma virus (HPV) types that are linked to the development of cervical cancer, the second most common cancer among women (see *VAX* February 2006 *Spotlight* article, *Cervical cancer vaccines*). These three researchers will share the US$1.4 million prize.

Barré-Sinoussi and Montagnier discovered the retrovirus now known as HIV in 1983, just two years after the first reports of cases described what is now known as AIDS. This critical finding paved the way for the development of methods to test for and diagnose HIV infection and eventually led to the development of antiretroviral drugs to treat HIV. *—Andreas von Bubnoff*

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What are the limitations of the animal models used by researchers to evaluate AIDS vaccine candidates?

In the hunt for treatments and prevention tools against pathogens such as HIV, scientists often turn to animal models for insights into how the virus establishes infection and causes disease. Through the study of infection with simian immunodeficiency virus (SIV)—a monkey virus that is similar but not identical to HIV, which infects many species of nonhuman primates—researchers have uncovered several clues about how the virus is transmitted, the events following infection, and the hallmarks of disease progression or pathogenesis. There is also much to be learned from the study of SIV infection in species of nonhuman primates that can successfully control SIV infection and not develop the monkey equivalent of AIDS (see *VAX* September 2008 *Primer* on *Understanding Control of Virus Replication).*

Animal models are also one of the best ways to evaluate the safety and efficacy of new medicines or vaccine candidates, serving as a bridge between laboratory evaluation and clinical trials, which involve human volunteers. But finding an animal model for HIV has proven difficult. The virus exclusively infects and causes disease in humans, making it more difficult for scientists to evaluate potential AIDS vaccine candidates.

SIV vs. SHIV

However, there are many similarities between HIV and SIV and most researchers agree that studying SIV infection in nonhuman primates, particularly rhesus macaques, is so far the best model of HIV infection in humans. In rhesus macaques, SIV infection tends to follow a similar disease course as HIV. SIV-infected rhesus macaques have very high levels of virus circulating in their blood and also develop a marked decline in the number of $CD4^+$ T cells, critical immune cells that are the primary target of both SIV and HIV. But in order to evaluate AIDS vaccine candidates in macaques, researchers must reconstruct the candidates to include non-infectious fragments of SIV, rather than HIV.

Due to this limitation, researchers have also constructed viruses that more closely mimic HIV. These hybrid viruses, known as SHIV, are a combination of SIV and HIV. SHIV was originally thought to be a better virus for evaluating the efficacy of AIDS vaccine candidates in nonhuman primates because it contained parts of HIV, but this has not been the case so far.

For instance, Merck's Adenovirus serotype 5 (Ad5)-based vaccine candidate, known as MRKAd5, did show some degree of efficacy against SHIV in nonhuman primate studies. However similar results were not seen when this vaccine candidate was tested in the STEP trial, a Phase IIb test-of-concept study involving 3,000 volunteers. The Ad5 candidate had no effect on virus levels in vaccinated volunteers who subsequently became HIV infected through natural exposure to HIV, indicating that the SHIV model in rhesus macaques was not predictive of the response in humans. Preclinical studies with MRKAd5 in monkeys showed that it was not effective against SIV, which suggests this may be a more accurate model for evaluating vaccine efficacy.

Results from the STEP trial have sparked a debate among researchers about the role of nonhuman primate studies in AIDS vaccine research and development, with some arguing that some level of efficacy in the SIV/macaque model should be shown before an AIDS vaccine candidate is evaluated in clinical trials.

Mighty mice

In the meantime, researchers are also focusing on other animal models that may be useful in evaluating AIDS vaccine candidates. Mice are one of the most commonly used animal models in all of medical research, but their use in HIV research is severely limited by the fact that they also cannot be infected with HIV. However, this could change. Researchers are now developing a novel type of mice that can be infected with HIV.

This new animal model involves the use of mice that are genetically altered so that they do not have an immune system and can therefore accept transplants of human cells. The human cells then develop inside the mice, creating a miniature human immune system. These so-called humanized mice have been in development for decades and during this time researchers have made substantial improvements to their immune systems. The latest batch of humanized mice in development can be infected with HIV and develop immune responses to the virus that are quite similar to those seen in HIV-infected people.

These humanized mouse models are now being used to study HIV transmission and pathogenesis and to evaluate the efficacy of new antiretrovirals for the treatment of HIV infection. But the immune responses to HIV are very complex and researchers have to do some additional fine-tuning to the humanized mouse models before it can be used as a reliable screen for AIDS vaccine candidates prior to entering Phase I clinical trials.

However, even after further optimization, the humanized mouse model will still have several limitations. A chief challenge is the small size of a mouse compared to a human. A key component of the human immune system is the movement or trafficking of different immune cells throughout the body, and this will be dramatically different in a small mouse. Researchers also have to take smaller blood samples from mice, which limits their ability to analyze immune responses in these animals.

Beyond mice

Some researchers are also exploring using human tissues that are grown and sustained in the laboratory, rather than in a living organism, as a way to evaluate immune responses induced by different vaccine candidates. This method is known as an *in vitro* immune system and it too could be used in the future to preclinically evaluate AIDS vaccine candidates. Until then, the nonhuman primate/SIV model will likely remain the most trusted animal model for evaluating AIDS vaccine candidates.