October 2006 • Vol.4 • No.10

VAX

AIDS VACCINE BULLETIN • WWW.IAVIREPORT.ORG

Spotlight

A shot of good news

Promising results from clinical trials presented at this year's AIDS Vaccine conference.

The near thousand researchers who gathered at the start of the annual AIDS Vaccine Conference in Amsterdam from August 29 to September 1 were greeted with a spirit of optimism that has become quite unusual for this field. Lawrence Corey of the HIV Vaccine Trials Network in Seattle called 2006 "a vintage year for vaccine development" when he gave a presentation on the AIDS vaccine pipeline at the conference's opening plenary session.

The source of Corey's enthusiasm was the data from several ongoing clinical trials showing that some AIDS vaccine candidates are inducing promising levels of cellular immune responses. "A few years ago it was hardly possible to stimulate T-cell responses with vaccination," said Andrew McMichael of the University of Oxford, UK, so this was a welcome shot of good news for a field that has struggled to develop candidates that are immunogenic in humans. Now Phase I and II trials with candidates based on adenovirus or poxvirus vectors are providing more encouraging results.

While efforts to stimulate a neutralizing antibody response with immunization are still largely unsuccessful, researchers have been able to increasingly improve the level of cellular immune responses. Those induced by the current crop of candidates are three times greater than was possible just a couple of years ago, said Corey. He is hopeful that this progress will continue over the next few years and that further improvements of candidates that induce potent cellular responses may bring the field closer to a partially-effective AIDS vaccine. This type of vaccine may either prevent HIV infection or, perhaps more likely, slow disease progression in those who do become HIV infected and lower the likelihood of them transmitting the virus to others.

But many researchers still question how effective an AIDS vaccine will be if it doesn't also induce neutralizing antibodies. Jaap Goudsmit of the Netherlands-based biotechnology company Crucell reminded researchers that there is yet to be a vaccine, for any disease, licensed solely on the basis of cellular immune responses. Therefore vaccines that induce neutralizing antibodies remain a focus of ongoing research.

Vintage data

Much of the promising immunogenicity data presented at the conference came from trials administering two different vaccine candidates sequentially in a prime-boost combination. Several different research groups are utilizing DNA plasmid vaccines for the initial immunization, which seem to effectively prime the immune system.

One of the earliest presentations on a DNA vaccine candidate was by Eric Sandström of the Karolinska Institute, Sweden, who presented for the first time immunogenicity data from a Phase I trial that is ongoing in Stockholm with a DNA vaccine developed at the institute in collaboration with the Swedish Institute for Infectious Disease Control (see *VAX* April 2006 *Spotlight* article, *Clinical trials march on*). Forty volunteers in the trial were randomized to receive three injections with one of three doses of the DNA vaccine administered either intramuscularly with a traditional injection or intradermally via the needle-less system developed by Bioject, a US-based biotechnology company.

Six months after the third DNA immunization all but two volunteers also received a booster immunization with a modified vaccinia Ankara (MVA)-based vaccine candidate developed by the US National Institutes of Allergies and Infectious Diseases. Vaccine recipients reported experiencing fatigue and general flu-like symptoms after the DNA prime and only mild adverse events were reported after the MVA injection.

After the third DNA immunization, 11 of the 38 volunteers were considered to have positive immune responses. But after receiving the booster immunization, 33 of 36 participants had positive results. Based on the impressive immunogenicity of these candidates, Sandström and colleagues are preparing for a larger Phase I/II trial in Tanzania with the same vaccine candidates.

Results from a Phase I trial conducted by the European Vaccine consortium (EuroVacc) with another DNA plasmid

In This Issue

vaccine tested in combination with a modified poxvirus vector vaccine, known as NYVAC, were also presented. A total of 40 volunteers—20 male, 20 female—were recruited at two sites in the UK and in Switzerland. Half of the participants received two injections of a DNA plasmid vaccine followed by two doses of NYVAC. Of the 20 volunteers who received the DNA/NYVAC prime-boost combination, 90% had positive immune responses.

Rick Koup also presented an update on the DNA plasmid vaccine and adenovirus serotype 5 (Ad5) vector-based vaccine developed by the Vaccine Research Center (VRC) at the US National Institutes of Health (NIH) that are currently in Phase I/II clinical trials in a prime-boost regimen (see *VAX* April 2006 *Spotlight* article, *Clinical trials march on*). Enrollment for these trials is now two-thirds complete but is still ongoing at HIV Vaccine Trials Network (HVTN) sites in North and South America and South Africa and at Walter Reed Army Institute of Research (WRAIR) sites in Africa. In the meantime the VRC, WRAIR, and IAVI are preparing to move these candidate vaccines into a Phase IIb test-of-concept trial, known as PAVE 100, which should commence next year.

Nature's adjuvant

Adenovirus-based vaccine candidates have produced the most impressive cellular immune responses seen so far, and Gary Nabel of the VRC referred to the viral vector as "nature's adjuvant," (see *VAX* October 2004 *Primer* on *Understanding Vaccine Adjuvants*). Another advantage of this vector is that it can be administered at much higher doses than other viral vectors—1000 to 10,000-fold more viral particles than can be safely used with MVA, for example.

But results from a Phase I safety trial, HVTN 054, indicate that vaccination with higher doses of Ad5 results in more severe side effects without any further gain in immunogenicity. Laurence Peiperl of the University of California, San Francisco presented data from this trial that evaluated a single injection of the VRC's Ad5 vaccine candidate at a low and high dose. Flu-like symptoms or reactions at the injection site were reported in four volunteers, all of whom received the higher dose. These side-effects peaked one or two days following injection and subsided within a week. Although none of the serious adverse events were considered related to the vaccine, Peiperl concluded that the safety profile of the lower dose seemed more favorable. Additionally the immune responses were actually higher in volunteers who received the lower dose—95% were considered responders compared to 90% at the higher dose. "It appears that less is more for immune responses to adenovirus," said Robert Seder of the VRC.

> ***The next few years are going to be very interesting in this field. There is a lot of energy right now about new prevention strategies and hopefully we will have good news on T-cell based vaccines.***
>
> **Michael Robertson**

Merck is currently evaluating the immunogenicity of the lower dose of their Ad5 vaccine candidate in the company's ongoing Phase IIb test-of-concept trial in collaboration with the HVTN (see *VAX* October 2005 *Spotlight* article, *AIDS vaccine researchers find promise*). The highly anticipated efficacy data from this trial won't be available until 2008 but Michael Robertson of Merck provided some preliminary information about the safety of the vaccine candidate. The majority (74%) of volunteers reported mild or moderate adverse events, most of which were headache, fever, fatigue, or pain at the injection site. Serious adverse events occurred in 13 individuals and 3 of these were attributed to the vaccine, including a severe case of fever, diarrhea, and a report of a possible allergic reaction.

Another focus of his presentation was on the experiences of conducting the trial in individuals at high risk of HIV infection either through sexual activity or injection drug use. Conducting trials in these populations will allow researchers to get preliminary efficacy results with smaller, faster, and less expensive studies, a strategy advocated in IAVI's *AIDS Vaccine Blueprint 2006* (see *VAX* September 2006 *Global News*). But some have speculated that it will be more difficult to both recruit and retain high-risk individuals in long-term vaccine trials, said Robertson. So far, at least, this has not been Merck's experience. Almost 2000 volunteers—1329 male and 668 female—were enrolled in the study at the end of July and, overall, 95% of scheduled visits have been completed. Robertson expects enrollment of the intended 3000 total volunteers to be completed on target by the end of this year.

Merck is gathering information on the risk behaviors of potential volunteers and Robertson presented some of this data. Across all sites, male volunteers screened so far for the Phase IIb study reported having a median of six different sexual partners in the last six months, and 12% of them reported having unprotected anal intercourse with a partner who they knew was HIV infected. Women reported having an average of 28 different sexual partners over the previous 6 months and 5% said they had unprotected vaginal intercourse with an HIV-infected partner. Also, 15% percent of the women reported having another sexually-transmitted disease in this same time period, which can enhance their risk of becoming HIV infected. During the screening process the HIV prevalence rates among males was 4% and around 3% for females, though Robertson explained that these figures vary greatly from site to site.

The AIDS vaccine field is eagerly anticipating the results of this and other ongoing trials to answer some of the critical questions about cellular immunity. "The next few years are going to be very interesting in this field," said Robertson. "There is a lot of energy right now about new prevention strategies and hopefully we will have good news on T-cell based vaccines."

Global News

Phase I AIDS vaccine trial in infants begins in Uganda

Researchers at Makerere University in Kampala, Uganda, in collaboration with Johns Hopkins University in the US, recently initiated the first Phase I trial of an AIDS vaccine aimed at preventing the transmission of HIV from mother to child during breastfeeding. According to the World Health Organization breastfeeding remains one of the major routes of HIV transmission to infants in developing countries. In many settings alternatives to breastfeeding, such as liquid formula or powdered milk, are either prohibitively expensive or impractical because they require access to clean water. In many cultures where breastfeeding is common practice, HIV-infected women who do not breastfeed their babies are also subjected to stigma.

Several studies have shown that treating HIV-infected women with antiretrovirals during late pregnancy, labor, and through the breastfeeding period is an effective way to prevent HIV transmission to infants, but not all women have access to these drugs (see *VAX* February 2005 *Spotlight* article, *Preventing mother-to-child transmission*). A vaccine that could effectively protect babies during the period they are breast fed would be a major advance.

The current trial will enroll 50 infants born to HIV-infected mothers at Mulago Hospital in Kampala and evaluate the safety of the vaccine candidate ALVAC-HIV vCP1521 as compared to placebo. Forty of the infants will receive four doses of the vaccine over three months and will be followed by researchers for two and a half years. The vaccine candidate, based on a canarypox virus carrying genetic pieces of HIV, was developed by Sanofi Pasteur and was already tested in a safety trial in Uganda involving adult volunteers and in another study involving infants in the US. No serious safety issues were reported in either of these previous trials.

ALVAC vCP1521 is also now being tested in a Phase III efficacy trial in Thailand to see if it can protect adults against HIV infection. The Thai trial recently completed enrolling volunteers but final results will not be available for a few years.

For more information on these and other ongoing trials, go to www.iavireport.org/trialsdb.

New global vaccine conference to accompany annual Grand Challenges for Global Health meeting

Grant recipients through the Grand Challenges in Global Health Initiative, a US$436.6 million program funded by the Bill & Melinda Gates Foundation to increase research on diseases that primarily affect developing countries, recently convened their annual meeting in Washington, DC to highlight progress on the 48 ongoing projects. Grantees include scientists from 33 countries who are working to tackle either scientific or technological challenges that could enhance global public health (see www.gcgh.org for more information). The plans for this innovative funding mechanism were initially announced at the World Economic Forum in 2003 and the first round of grants were awarded last year in collaboration with the US National Institutes of Health.

The Gates Foundation also recently awarded the Keystone Symposia on Molecular and Cellular Biology, a US non-profit organization that hosts many high-profile scientific conferences, a three-year grant of $2.6 million to further expand their offerings of conferences that focus on global health. Keystone already sponsors several conferences concerning infectious diseases, including the annual symposia on HIV Pathogenesis and HIV Vaccines that are held in conjunction each spring.

With this new grant Keystone will add a meeting focused on vaccines called "Challenges of Global Vaccine Development," which will be held either immediately before or after the next Grand Challenges in Global Health Meeting. The first annual conference will take place from October 8-13 next year in Cape Town, South Africa and will involve 300 scientists, many of whom are investigators on one of the Grand Challenges projects. The Keystone Symposia will also use part of the grant to provide scholarships and travel awards to researchers from developing countries, and specifically to graduate students and post-doctoral fellows who are completing their studies in Africa.

Other meetings that will be launched next year with this new funding include, "HIV Vaccines from Basic Research to Clinical Trials" and "Molecular and Cellular Determinants of HIV Pathogenesis."

VAX

Editor
Simon Noble, PhD

Science Writer
Kristen Jill Kresge

Production Manager
Nicole Sender

All articles written by Kristen Jill Kresge.
VAX is a project managed by Kristen Jill Kresge.

iavi
International AIDS Vaccine Initiative

FREE SUBSCRIPTIONS:

If you would like a personal subscription to *VAX* by e-mail, please send a request, including language preference, to iavireport@iavi.org. Or if you would like to receive multiple print copies of *VAX* (English version only) to distribute and/or use in your programs, please send your request, including number of copies and full postal address, to iavireport@iavi.org.

For more information, go to www.iavireport.org.

VAX is a monthly bulletin from *IAVI Report*, the publication on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, German, Spanish, and Portuguese as a downloadable pdf file (www.iavireport.org) or an e-mail bulletin.

IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

How are AIDS vaccine candidates tested for safety and immunogenicity before they enter clinical trials?

Clinical trials are a stepwise process to determine the safety and immunogenicity of AIDS vaccine candidates in human volunteers. The earliest trials (Phase I and II) are designed primarily to evaluate safety, while the later stage trials (Phase IIb and III) are when researchers determine if the vaccine candidate is effective. Each Phase involves a progressively larger number of volunteers and conducting clinical trials is a time-consuming and expensive process. The conduct of these trials is closely monitored by regulatory agencies, like the US Food and Drug Administration or the European Union's European Agency for the Evaluation of Medicinal Products, to ensure that a vaccine candidate meets necessary safety standards.

Prior to testing in humans, vaccine candidates are developed and tested extensively by researchers in the laboratory and then in different animal models. Data from these pre-clinical studies give researchers important information about how vaccine candidates might work in people and are carefully reviewed by regulators when they are granting approval to an organization or company to proceed with a Phase I clinical trial.

Vaccine development

Before a vaccine candidate is tested using animal models, researchers fully characterize the engineered vaccine in the laboratory—whether it is a viral vector, protein subunit, or DNA-based vaccine that will be used to present HIV protein to the immune system. For candidates that use viral vectors (see *VAX* September 2004 *Primer*, *Understanding Viral Vectors*), scientists will already have an extensive body of knowledge about how the naturally-occurring virus acts both biologically and immunologically so that they have an idea of how it will act in humans. This allows researchers to generate a well-informed hypothesis about the types of immune responses the vaccine candidate might induce in humans.

Other pre-clinical evaluations

Even with a strong hypothesis, laboratory studies can only give researchers a vague idea of how the vaccine will work in the complex environment within the human body.

To try to gauge the safety and immunogenicity of a vaccine candidate, therefore, scientists have to conduct research in animal models. Usually the vaccine candidate will first be tested in mice and then in non-human primates, most often rhesus macaques.

Researchers start by administering the vaccine candidate to macaques and then characterizing the immune response it induces. This includes a detailed analysis of the cellular responses, especially in T cells, and measuring the level and type of antibody responses. Based on these results researchers can alter the vaccine candidate to try to enhance its immunogenicity and then re-test it in macaques. Working with animal models allows researchers to obtain extensive data that would be impossible to collect from human volunteers.

Next researchers usually use challenge studies to evaluate vaccine candidates. In these studies the vaccine candidate is administered to macaques that are later infected with simian immunodeficiency virus (SIV), which naturally infects many species of non-human primates. Challenge studies are only conducted in animal models, never in human volunteers. In this type of study researchers can determine how many macaques are protected by the vaccine candidate from becoming infected with SIV. They can also determine how long this protection lasts by challenging the macaques again later. Challenge studies may also provide clues on what type of immune responses (specific types of antibodies or cellular responses) are responsible for this protection, an idea referred to as correlates of protection.

This data gives researchers critical information about the vaccine candidate and helps them determine if it is safe and immunogenic enough to move into clinical trials involving human volunteers. Many of the vaccine candidates that are evaluated in pre-clinical studies never actually advance into clinical trials because they are not immunogenic enough to explore further.

Limitations

One important limitation with these animal studies is that the vaccine is not being tested against an HIV challenge. Researchers must evaluate the vaccine candidate's immunogenicity against SIV, which is a closely-related but different virus, because HIV does not infect non-human primates. To more closely mimic HIV infection in humans, researchers have tried running challenge studies with an engineered virus that contains both SIV and HIV genes—known as SHIV—but this is generally seen as an even less satisfactory model than SIV for predicting how a vaccine will work in humans.

Another limitation is that researchers have to also modify the vaccine candidate to carry SIV genes, rather than HIV genes, to match the virus being used in the challenge studies. Using a different challenge virus and a different vaccine candidate in a different animal species makes pre-clinical evaluation more difficult. This is just one of the many complications researchers face in developing an effective AIDS vaccine.

For many years, therefore, researchers have sought ways to improve their ability to evaluate candidates in pre-clinical studies and find a better animal model for HIV infection. Recently researchers have developed an engineered mouse model where human cells are transplanted into mice that have their own immune systems depleted. This allows mice to grow human immune cells that can be infected by HIV. With refinement this type of model may be useful to researchers as an initial screen for AIDS vaccine candidates to help determine if a candidate is immunogenic enough to pursue in human clinical trials.

Scientists are also studying the genetic factors that allow non-human primates to fend off HIV infection. This research might one day enable scientists to engineer an HIV strain that can productively infect an animal model and therefore more closely mimic human infection.