

# VAX

AN IAVI REPORT  
BULLETIN

[www.iavi.org](http://www.iavi.org)

VAX is a monthly bulletin featuring shorter, non-technical versions of articles from the *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative. VAX is currently available in English, French, Spanish and Portuguese as a pdf ([www.iavi.org/iavireport](http://www.iavi.org/iavireport)) or an e-mail bulletin. If you would like to receive VAX by e-mail, please send a request including language preference to: [VAX@iavi.org](mailto:VAX@iavi.org)

Re-publication and re-distribution of VAX articles in their entirety is welcome, with the following credit line: This article was reprinted from the Month/Year issue of VAX, published by the International AIDS Vaccine Initiative ([www.iavi.org/iavireport](http://www.iavi.org/iavireport)). A VAX template is also available for groups that would like to produce their own editions, combining VAX articles with local content. For more information, email [VAX@iavi.org](mailto:VAX@iavi.org)

FEBRUARY 2004  
Vol.2 ■ Num.1

## In this issue

### RESEARCH & TRIALS

- ◆ IAVI and Partners Begin Two Phase I AIDS Vaccine Trials
- ◆ Chiron Begins Phase I AIDS Vaccine Trial
- ◆ Vaccines at Retrovirus Conference 2004

### GLOBAL NEWS

- ◆ Major New Grant for Tuberculosis Vaccine Research

### SPOTLIGHT

- ◆ How Might Other Diseases Affect AIDS Vaccine Trials?

### PRIMER

- ◆ Understanding the Immune System

## RESEARCH & TRIALS

### ◆ IAVI and Partners Begin Two Phase I AIDS Vaccine Trials

IAVI, in partnership with industry and academic research centers, began two separate AIDS vaccine human trials in December 2003. The trials are testing two different vaccine candidates that will try to prevent HIV infection. The first trial is a collaboration between IAVI and the Aaron Diamond AIDS Research Center (ADARC), an affiliate of Rockefeller University (New York). The vaccine being tested is a new DNA vaccine called ADVAX and contains synthetic fragments of **clade C** HIV genetic material. None of the vaccine components can cause HIV infection. Clade C is the most common subtype of HIV in the world and is found in China, India and in sub-Saharan Africa. Forty-five healthy non HIV-infected men and women will participate in the study, which will test the safety and **immunogenicity** of the vaccine.

The second trial is a collaboration between IAVI, Targeted Genetics Corporation and Columbus Children's Research Institute, and will be tested in Germany and Belgium. This is the first AIDS vaccine trial to take place in Germany. It is testing a vaccine called tgAAC09 AAV that contains fragments of clade C HIV genetic material within the

**Clade:** A group of genetically-related forms of HIV. Clades are also called genetic subtypes and generally have geographic distribution patterns. For example, clades A and D are most common in east Africa; clade B HIV is found in North America and Europe. sample of the volunteer's blood.

**Immunogenicity:** The strength of the immune responses produced by a vaccine; these immune responses are measured through laboratory tests on a sample of the volunteer's blood.

outer coating of a virus called adeno-associated virus (AAV) The coating has been stripped off AAV; the actual virus is not used in the vaccine. None of the vaccine components can cause HIV infection. All together, the trial will enroll up to 50 volunteers.

### ◆ Chiron Begins Phase I AIDS Vaccine Trial

In December 2003, the Chiron Corporation began its first trial of a preventive AIDS vaccine strategy. Chiron is co-sponsoring the trial with the US National Institute of Allergy and Infectious Diseases. The trial will be conducted by the US HIV Vaccine Trials Network (HVTN) and will enroll 168 volunteers at 10 sites in the US. The trial will test the safety and immunogenicity of a combination of two vaccines given at different times. This is called a "prime-boost" strategy; it is hoped that this strategy will produce a broader range of immune responses than either of the vaccines used alone. The first vaccine is called DNA/PLG and it contains synthetic fragments of clade B HIV genetic material. The second vaccine is called gp140. It is a copy of a part of the "envelope" or outer coating of HIV. Neither vaccine contains material that can cause HIV infection.

### ◆ Vaccines at Retrovirus Conference 2004

The 11th Conference on Retroviruses and Opportunistic Infections took place in San Francisco from 8-11 February and was attended by over 3,500 researchers and activists from around the world. The main focus of the annual meeting is basic science of retroviruses (a family of viruses that includes HIV) and HIV treatment and care, but this year there were also several sessions that looked at the current state of AIDS vaccine research. Researchers presented data on a variety of topics including chal-

A PUBLICATION OF THE IAVI REPORT

[ The Newsletter of the International AIDS Vaccine Initiative ]

lenges to developing vaccines that will strongly produce **neutralizing antibodies** (see *Primer*) against HIV; lessons learned from the large-scale AIDS vaccine trials to date; and how to best use the funds available for AIDS vaccine research.

Stephen Lewis, United Nations special envoy to Africa, gave a keynote address in which he said, "It is important to note that there are more potential vaccines in the pipeline than ever before." Lewis went on to say that "an AIDS vaccine is also a women's issue" since an effective vaccine would give to women "the ultimate protection from HIV infection without the male partner... having any involvement." Lewis singled out the work of IAVI and said that "much more" activity was needed from the pharmaceutical industry and government-sponsored research.

**Neutralizing antibodies:** Immune defenses that coat the surface of foreign invaders (such as HIV) in the blood. Neutralizing antibodies prevent the invader from multiplying itself or infecting cells.

## GLOBAL NEWS

### ◆ Major New Grant for Tuberculosis Vaccine Research

In February the Bill and Melinda Gates Foundation announced a US\$82.9 million grant to fund the search for a vaccine to prevent tuberculosis (TB). The grant is the largest ever for TB vaccine research. It was given to the Aeras Global TB Vaccine Foundation, a US-based research organization that is developing two TB vaccine candidates. Currently, the only available vaccine against TB, called BCG, primarily protects infants and young children against severe TB; it does not work as well in adults. The search for a TB vaccine has been slow due to lack of funding and lack of involvement on the part of major pharmaceutical compa-

nies—some of the same factors which have also slowed AIDS vaccine research. TB is one of the leading causes of death in people infected with HIV, and an effective TB vaccine is urgently needed. Dr. Jerald Sadoff, president of Aeras, says that it will take eight to ten years to evaluate these vaccine candidates and make them available, if they prove effective.

## SPOTLIGHT

### ◆ How Might Other Diseases Affect AIDS Vaccine Trials?

**AIDS** is the single most serious health threat in the world today. But at the same time, there are many other illnesses that pose major problems in several regions that also have severe AIDS epidemics including sub-Saharan Africa, Asia and Latin America. Other widespread diseases include worms (also known as helminthic infections or intestinal parasites), tuberculosis, malaria and sexually transmitted diseases other than HIV. To be effective, an AIDS vaccine will have to provide protection to people who are (or have been) infected with other diseases. This is one reason why AIDS vaccine trials are being conducted in these regions of the developing world. These trials will provide valuable information about how other diseases might affect AIDS vaccine trials.

This is a relatively new focus for any field of vaccine research. Many of today's vaccines, including those against polio and measles, were approved based on the results of large trials in the US and Europe where healthcare systems are generally effective and diseases like tuberculosis are relatively uncommon. After approval, these vaccines were eventually distributed worldwide and reached people living in resource-poor settings. It was only at this stage that researchers began to gather information on how people in developing countries respond to the vaccines.

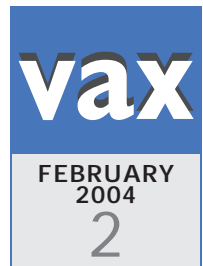
More recent vaccines, such as those targeting *Streptococcus pneumoniae* (which causes pneumonia and meningitis) and hepatitis B, were

evaluated in developing countries including South Africa and Thailand. But the AIDS vaccine field is the first to include developing countries at

every stage of vaccine testing—from small safety studies to large-scale efficacy trials. There are several reasons for this focus. First, some of the highest rates of new HIV infections per year are found in the developing world. AIDS vaccine efficacy trials need to be conducted in places with high rates of HIV infection if they are to provide rapid answers about whether or not a vaccine provides protection. These trials test a vaccine by comparing the number of HIV infections (through high-risk contact such as unprotected sex) in a group of volunteers who are given the vaccine with the number of infections in a group given an inactive substance called a **placebo**. This comparison can be made most rapidly in communities where there are high numbers of new HIV infections each year.

Second, these trials will provide information about how AIDS vaccine candidates will work in the places where they are most urgently needed: developing countries where poverty, poor healthcare and high rates of other diseases are part of many people's daily lives.

This is important information to collect since there is evidence that some vaccines work differently in people in developing countries when compared to people in developed countries. In some small studies of cholera vaccine, BCG vaccine (which protects against tuberculosis), tetanus toxoid, and oral polio vaccine, people living in developing countries had lower immune responses to these vaccines when compared to people in the industrialized world who received the same vaccine. One possible explanation for these differences



**Placebo:** An inactive substance given to some AIDS vaccine trial participants, while others receive the experimental vaccine.

lies in the fact the **immune system** mounts specific responses to every infection that occurs in the body (see **Primer**). Pre-existing immune responses to other infections might affect people's ability to mount responses to these vaccines.

This does *not* mean that these vaccines do not work in developing countries. According to these studies, increasing the vaccine dose given to people in the developing world usually boosts their immune responses. However it does mean that AIDS vaccine trials must learn about other pre-existing infections in people who participate in trials or will someday use a licensed vaccine.

The Soweto Vaccine Evaluation Unit at Chris Hani Baragwanath Hospital in South Africa recently conducted a study in which they tested over 100 potential AIDS vaccine trial volunteers for helminthic infection. Some studies have shown a connection between infection with these and other worms and reduced responses to vaccines such as tetanus toxoid, BCG and oral cholera.

"Helminth infection and exposure to other types of worms occurs more commonly in Africa than in developed countries. We are interested in how many adults from Soweto have such infections," says Guy De Bruyn, one of the South African scientists conducting the study.

De Bruyn says that if the Soweto study finds high levels of helminthic infections, the site may test future AIDS vaccine trial participants for worms and, if necessary, provide anti-worm medication before administering the AIDS vaccine candidate.

#### **Health and trial participation**

All volunteers for all preventive AIDS vaccine trials receive an HIV test before enrollment, since volunteers must be uninfected with HIV when the trial begins. The other compo-

**Immune system:** A complex system of cells and substances that work together to protect the body from infections and illnesses.

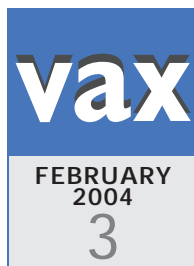
nents of the health screening process vary depending in the type of trial.

Small Phase I safety studies are designed to confirm that the vaccine is completely safe for use in humans

These trials also measure volunteers' immune responses to vaccines. All Phase I trial volunteers undergo a lengthy health screening process. This includes an analysis of volunteers' blood samples, so that trial staff have a good understanding of volunteers' immune responses and general health status before the trial starts. Phase I participants are closely monitored throughout the study and trial staff make precise diagnoses of any health problems that occur among volunteers. For example, a feverish patient from a community with high rates of malaria would have his or her blood tested to confirm malaria infection—even though a doctor might ordinarily prescribe anti-malarial medications based on the symptoms alone. By pinpointing the cause of all health complaints in Phase I trials, vaccine developers can make reliable statements about the safety of the candidate vaccine.

In the next stage of larger trials (Phase II and Phase III) volunteers undergo a shorter health screening process. Volunteers are still tested for HIV and other severe illnesses, but they may not be screened for mild conditions or "asymptomatic" conditions that they may be unaware of, such as low-grade malaria, worms or anemia. By testing the vaccine in this population, vaccine developers get a better idea of whether or not some common conditions will impact on how the vaccine works.

If a vaccine shows efficacy in Phase II and Phase III trials then vaccine developers will conduct follow-up studies to learn even more about how the vaccine works in people with more complex health issues. Vaccine developers will only seek approval for the vaccine after this lengthy but important process has been completed. So far, no AIDS vaccine candidate has reached this stage of development.



EDITOR

Simon Noble, PhD

SENIOR WRITER

Emily Bass

PRODUCTION

Michael Hariton

WEB EDITOR

Roberto Fernandez-Larsson, PhD

DESIGN

DESIGNdeFrancesco.com

The Spotlight in this issue of VAX is based on an article by Emily Bass which originally appeared in the September 2003-January 2004 issue of the *IAVI Report*. All other articles are by Emily Bass.



VAX is a monthly bulletin from the *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, Spanish and Portuguese as a pdf ([www.iavi.org/iavireport](http://www.iavi.org/iavireport)) or an e-mail bulletin. If you would like to receive VAX by e-mail, please send a request including language preference to: [vax@iavi.org](mailto:vax@iavi.org)

IAVI is a global organization working to speed the development and distribution of preventive AIDS vaccines—the world's best hope for ending the AIDS epidemic. IAVI focuses on four areas: mobilizing support through advocacy and education, accelerating scientific progress, encouraging industrial participation in AIDS vaccine development and assuring global access.

Copyright © 2004

# HOW DO VACCINES INTERACT WITH THE IMMUNE SYSTEM?

vax

FEBRUARY  
2004

4

## The immune system and protection from disease

The immune system is the set of defenses in the body that protects us from becoming ill. It is made up of many different types of cells and substances, all of which work together to help us heal when we have been injured, get well when we have become ill, and avoid some illnesses altogether.

The immune system can do this because it is able to recognize, fight and remember foreign invaders, like bacteria or viruses, which can cause illness when they enter the body. Such invaders are called "pathogens." A common cold is caused by a pathogen (a cold virus). HIV is the pathogen that causes AIDS.

When a new pathogen enters the body, the immune system uses a variety of defenses to control or get rid of it. One of the first responses comes from B cells. These cells can recognize foreign invaders soon after they have entered the body, but before they have entered and infected any of the body's cells. Many pathogens, including HIV, enter cells and infect them in order to multiply.

B cells produce antibodies which coat the surface of the pathogen to stop it from multiplying itself or infecting cells. This process is called "neutralization." Antibodies also label the pathogen so that other immune defenses can "see" and attack it.

Another initial response comes from other immune system cells called dendritic cells and macrophages. These cells patrol the body and pick up the pathogen. They then carry the pathogen to the lymph nodes, which are the hubs of the immune system. Lymph nodes can be found under the jaw, under the arms, in the gut and in the groin. When we start becoming ill, our lymph nodes often become swollen or sore as immune cells gather in the nodes to fight the infection.

In the lymph node, the patrolling cells show or "present" the pathogen to CD4<sup>+</sup> T cells. These "helper" CD4<sup>+</sup> T cells coordinate the activities of a set of "killer" cells called CD8<sup>+</sup> T cells. CD4<sup>+</sup> and CD8<sup>+</sup> T cells work together to eliminate cells that have been infected by pathogens.

HIV infects and kills CD4<sup>+</sup> T cells, which is why doctors sometimes count these cells when people are infected with HIV. Our immune systems try to fight off HIV by sending CD8<sup>+</sup> T cells to kill off the HIV-infected CD4<sup>+</sup> T cells. Unfortunately the immune system cannot eliminate HIV from the body. Over a period of time, HIV infection exhausts the body's immune defenses. This leaves HIV-infected people vulnerable to a variety of other infections. Antiretroviral drug treatment can suppress multiplication of the virus in the body and so reduce HIV-related illness, prolonging the life of the infected person. But this treatment cannot rid the body of HIV completely.

## Immune memory

Although the immune system cannot control HIV, it can control or get rid of many other infections. This is why we become well after many illnesses. After a pathogen has been controlled, most of the

immune cells and antibody that fought the infection disappear. However a small group of "memory" immune cells remains in the body. These memory cells have already fought the pathogen once before and so if the pathogen ever enters the body again they can very quickly start a strong immune response. Memory cells "arm" the body against future infections from the same pathogen. There are some infections, such as chickenpox or measles, which we generally get only once. This is because memory cells from the first infection effectively fight the pathogen if we are ever exposed to it again.

## Vaccines and immune memory

Immune memory is a key reason why vaccines protect us from disease. An effective vaccine safely introduces the immune system to a pathogen that it has never seen before. It arms the immune system so that it can effectively control the pathogen if it ever invades the body. Vaccines use safe forms or fragments of pathogens to mimic the actual pathogen and trick the body into generating immune responses. The fragments or safe forms of pathogens that are used in vaccines are called "immunogens." This word reflects the fact that

vaccines cause immune responses, *not* disease.

When the vaccine enters the body, the immune system sees it and responds to it just as it does to any foreign substance. T cells and B cells react to the vaccine. Some of these cells become memory cells. These cells are ready to respond to the real pathogen if it ever enters the body.

All of the AIDS vaccines in development today use small fragments of HIV as their immunogens. These fragments cannot cause HIV infection. The goal of these experimental AIDS vaccines is to produce memory cells that will be able to mount a rapid, strong immune response against HIV if a person is ever exposed to whole, live HIV through high-risk contact such as unprotected sex.

Today the challenge for AIDS vaccine developers is to identify the best immunogens to create strong antibody and cellular responses that will protect against HIV infection and disease.

### ■ For more information:

*Fact sheets, animated videos and illustrations explaining the immune system:*

[www.thebody.com/whatis/underst.html#immune](http://www.thebody.com/whatis/underst.html#immune)

*The Science of HIV/AIDS Vaccines: An Introduction for Community Groups:*

[www.icaso.org/icaso/vaccines.htm](http://www.icaso.org/icaso/vaccines.htm)

*This is also available in plain text via email;*

*send request to:*

[icaso@icaso.org](mailto:icaso@icaso.org)

*This is the first in a series of Primers on the immune system. Future Primers will discuss the types of immune responses that might be able to control HIV, and the challenges in designing vaccines that lead to these responses.*

## PRIMER

### UNDERSTANDING

# the immune SYSTEM

Part I