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AN IAVI REPORT BULLETIN

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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, German, Spanish and Portuguese as a pdf (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

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In this issue

RESEARCH & TRIALS

Multi-clade Vaccine Trial Launched in Massachusetts

In April, scientists at the University of Massachusetts Medical School (US) started recruiting 36 healthy, HIV-uninfected volunteers for a Phase I trial of a preventive AIDS vaccine strategy. The vaccines being tested are a **DNA vaccine** and a **recombinant gp120** protein vaccine. Both of the candidates were developed by Dr. Shan Lu, associate professor of medicine and the head of the HIV vaccine effort at UMMS, in collaboration with Advanced Bioscience Laboratories. They are being tested in a "prime boost" strategy which uses two different vaccines given at different times.

Both of the vaccines are based on genetic material from four different versions, or clades, of HIV. This material is produced in a laboratory and cannot cause HIV. Clades are genetically-related families of HIV viruses. Different clades are found in different regions of the world.

It is not yet known whether it will be possible to make a single "universal" vaccine against all versions of HIV, or whether it will be necessary to make many different vaccines, each based on the most common versions of HIV in a given region. Data from this and other trials of "multi-clade" vaccines will increase understanding of how HIV genetic diversity affects vaccine design.

In an early Phase I trial, scientists will be able to conduct laboratory tests on volunteers' blood samples to see whether or not the immune responses produced by the vaccines control different versions of HIV. These tests will not provide a final answer but they will provide useful information about whether it is possible to generate "cross-clade" protection with a single vaccine.

DNA vaccine: A DNA vaccine against HIV consists of a molecule that closely resembles a fragment of the HIV genome (the genetic material that contains all of the information HIV needs to make copies of itself.) The fragment cannot cause HIV infection, but when it is introduced into the body it may still cause immune responses that can fight HIV.

gp120 (glycoprotein 120): gp120 is a molecule found on the outer surface (envelope) of HIV. gp120 binds to the CD4 molecule on helper T cells during infection. It has been studied as an experimental AIDS vaccine because the outer envelope is the first part of the virus "seen" by immune defenses called neutralizing antibodies.

Recombinant: Recombination is the process by which pieces of genetic material from two different sources are joined (spliced) together. A recombinant is the new genetic material that is formed or the protein(s) that it produces.

GLOBAL NEWS

Microbicides 2004 Conference Held in London

Over 700 people from over 50 countries gathered in London for Microbicides 2004 (March 28-31), the third bi-annual conference devoted to the search for a cream or gel that could be applied vaginally or rectally to block HIV infection. The field has grown significantly over the past four years and as many as six large-scale efficacy trials of microbicides are scheduled to begin in 2004. There are also over 60 candidates in various stages of pre-clinical and clinical development (see *Primer*).

Scientific presentations at the meeting highlighted challenges confronting the field. Several speakers focused on recent insights into how HIV infection occurs during sexual transmission. HIV can infect several different types of cells found in the "mucosal" surfaces of the vagina, cervix and rectum. This means that

the virus can take several different pathways into the body and that an effective microbicide will probably have to block infection of a number of different types of cells.

Other presentations explored ethical issues surrounding microbicide trials, many of which also face AIDS vaccine trials. Challenges include how to ensure that trial volunteers who become infected with HIV receive high quality treatment and care; and when and how to involve the male partners of women volunteers. (A full report on the state of microbicide research will appear in an upcoming issue of *VAX*).

SPOTLIGHT

◆ AIDS Vaccine Manufacturing

Developing an AIDS vaccine is a complex task that involves many steps including laboratory experiments and clinical trials (see *Primer*). But identifying promising vaccine candidates is only part of the effort. Another major, often-overlooked area of AIDS vaccine development is the manufacturing process.

Many resources are needed to manufacture a vaccine. These include production facilities and specialized scientific equipment, highly-trained scientists and technicians, and supplies of the materials used to make the vaccine. These resources are needed long before a vaccine has proven effective and been licensed for widespread use because clinical trials cannot take place without sufficient, readily-available supplies of the candidate vaccine.

The AIDS vaccine field is paying increasing attention to manufacturing needs and has identified some key gaps in current resources. In 2003 many leaders in the AIDS vaccine field proposed an AIDS Vaccine Enterprise that would increase collaboration on key issues like manufacturing. In February 2004 the Enterprise working groups on manufacturing and product development began to draft a strategic plan to address needs in these areas.

The plan produced by the Enterprise will be an important effort to address shortages in manufacturing resources that could slow down the pace of clinical trials or even delay access to an effective AIDS vaccine once it has been developed.

Making vaccines

Drugs are usually produced by combining a variety of chemical compounds. But vaccines are made using biological systems, meaning that living organisms are used to produce the vaccine. Vaccine developers take advantage of the fact that animal cells and bacteria produce many different substances as part of their normal functions, and adapt these capabilities to help make vaccines.

For example, DNA vaccines are copies of a small portion of HIV genetic material that cannot cause HIV infection. The most efficient way to make large quantities of these molecules is by getting microorganisms to produce them. Each microorganism functions like a miniature factory for the DNA vaccine.

From start to finish, it usually takes about nine months to produce a batch of vaccine. During this period, the vaccine is made, tested, packaged and labeled. Each step in this process is carefully monitored to ensure that the manufacturer meets international standards of "Quality Assurance" and "Quality Control." These international standards are applied to both experimental vaccines and to licensed products. They ensure that all vaccines are safe and of high-quality and that the product is made the same way each time.

Challenges: Process development and manufacturing capacity

Before a vaccine can be manufactured, scientists must precisely identify all of the steps in the production process and work out how best to carry them out. This is known as "process development." Most vaccines undergo several stages of process development. The first stage happens when a promising concept is identified in a laboratory and scientists develop a process to produce enough vaccine for trials in animals and, later, early trials in humans. The quantities of vaccine required for these safety trials are relatively small.

If a vaccine is shown to be safe in small-scale safety trials, it may then proceed to intermediate- and large-scale trials. The largest of these trials may enroll thousands of volunteers. At this stage the manufacturing process must be further developed to produce much larger quantities of vaccine.

Process development requires biotechnology experts. At the moment much of this expertise is concentrated within large pharmaceutical companies, many of which are not developing AIDS vaccines. Some AIDS vaccine developers are concerned that this lack of human resources could lead to delays in bringing potential vaccine candidates through clinical trials.

A second key gap is in manufacturing capacity, including facilities equipped to make the types of AIDS vaccines that are currently being tested in clinical trials. There are already limited facilities for producing licensed vaccines such as those that help prevent measles, mumps and polio. Additional new facilities are needed for experimental AIDS vaccines. These manufacturing facilities must have the ability to manufacture vaccines that are made using several different biological systems, since we still do not know which processes will be used to make an effective vaccine.

The need to plan ahead

It will likely be many years before there is an effective preventive AIDS vaccine. However vaccine developers must already begin to plan for the day when such a vaccine is identified through clinical trials. Around the world, there will be urgent requests for this vaccine. The only way to meet these demands will be through large-scale production facilities that are equipped to make the new vaccine.

These factories cannot be built overnight. It usually takes between five and seven years and hundreds of millions of dollars to build and "validate" a new facility to ensure that it functions properly and meets all international regulatory requirements, including Quality Control and Quality Assurance standards.

It is not known if any of the vaccines that are currently being tested in clinical trials will help to prevent HIV infection or disease. However the field cannot wait for this information to begin investing in large-scale facilities. Such a delay could costs millions of lives. Instead, vaccine developers must take the risk of investing in manufacturing capacity before they know whether or not a vaccine is effective.

No single AIDS vaccine developer can address all of the field's manufacturing capacity and process development needs. The strategic plan from the Vaccine Enterprise working groups could provide a starting point for increased collaboration and coordination throughout the field.

IAVI Report Online

THE NEWSLETTER ON INTERNATIONAL AIDS VACCINE RESEARCH www.iavireport.org

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- *IAVI Report* is very pleased to announce the launch of its new website. IAVI Report Online is a centralized source of information on all aspects of AIDS vaccine research and associated scientific disciplines—from basic science like molecular virology and immunology to more applied fields such as HIV prevention research.
- Updated daily with highlights from the day's HIV/AIDS news from around the world, plus a round-up of the latest published research relevant to AIDS vaccine development, IAVI Report Online is a one-stop resource for HIV researchers, advocates, policy makers, and anyone else with an interest in the progress towards an effective, preventive AIDS vaccine.
- IAVI Report Online is home to all of the current and archived articles from the print editions of *IAVI Report* and also *VAX,* a monthly non-technical bulletin available in 5 different language versions—English, French, German, Portuguese and Spanish. IAVI Report Online incorporates a new Early Edition feature that will publish *IAVI Report* articles directly to the web as soon as they are available, ahead of print publication.
- Visitors to the website will be able to subscribe to any of the IAVI Report products in a variety of electronic and print formats, all free of charge.
- Roberto Fernandez-Larsson, PhD, Web Editor of the IAVI Report Online, is a virologist by training and comes from *AIDScience* website where, as Senior Editor, he developed and headed the *Science* magazine-sponsored AIDS prevention and vaccine research site.

Highlights of IAVI Report Online

Articles: In-depth articles on current topics by *IAVI Report* writers and others.

Interviews: Important figures in the development of AIDS vaccines address relevant questions.

Five Languages: *VAX* issues are translated from English to French, German, Portuguese and Spanish

Primers: AIDS vaccine related questions answered in non-technical format to enable non-scientists to broaden their understanding.

HIV/AIDS News Headlines: Updated daily with major international news media headlines of interest to HIV research scientists and others, with a small excerpt or summary of the article and a link to the media source.

This week's HIV/AIDS Journal Headlines: Updated weekly, this section contains scientific papers chosen by the *IAVI Report* team as the most significant and relevant to AIDS vaccine research and associated disciplines.

Hot News Section: This section highlights the most relevant HIV/AIDS news of the week.

Special Features: Contains databases, posters, maps, anthologies, and other archived special projects.

Other features:
Calendar of Meetings

This Week's Researchers

Coming soon:
French, Spanish, Portuguese and German content pages: HTML versions of translated content and related links for our non-English speaking readers.

Reviewed HIV/AIDS research sites

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International AIDS Vaccine Initiative

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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.

HOW ARE VACCINES DEVELOPED?

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Vaccine development is a lengthy process of testing ideas and candidates with the goal of identifying a safe, effective vaccine that can be reliably and affordably produced and distributed to all who need it. The development process can be divided into five overlapping stages. These stages are common to all medicines, vaccines and microbicides. Scientists, manufacturing experts, policy makers and advocates work on many of these stages simultaneously with different candidates. It can take 10 years or more for one candidate to complete the first three phases and even longer to identify an effective candidate for licensure and widespread use. The five stages are described below using AIDS vaccines as an example.

Idea Generation and Basic Science

Vaccine development begins with "basic science," which includes experiments on and observation of various aspects of HIV and the immune system. Basic science research is carried out in laboratories in universities, research institutes and private companies. Scientists use various techniques to isolate the virus and human immune cells and to study the types of cells HIV infects, how it kills those cells, and what effects this has on other cell types. One general term for these studies is "*in vitro* assays." (*In vitro* means "in glass" in Latin and it is used for studies that are conducted outside of a living organism.) *In vitro* assays give scientists a chance to observe processes that usually happen inside the human body. Some basic science experiments study immune responses to HIV in small animals like mice. Basic science provides clues about how to develop better vaccines.

UNDERSTANDING
vaccine DEVELOPMENT

Pre-Clinical Development

Pre-clinical tests include tests of the purity and composition of the candidate, as well as very early measures of vaccine effects against HIV. Some of these tests are done *in vitro* and some have to be done in animals. (Tests in animals or humans are called "*in vivo*" experiments.) For example, scientists might try to design a vaccine that causes immune responses that effectively control HIV growth in cells. This can be tested by immunizing mice, then testing their immune cells *in vitro* to see if they stop HIV from growing. These and other experiments are used to gather early information about "immunogenicity," which is a measure of the types and strength of the immune response caused by the vaccine. If the candidate appears promising, additional tests are done in monkeys. Researchers give the monkey the experimental vaccine and later "challenge" the animal with a monkey version of HIV called simian immunodeficiency virus (SIV) to see whether the vaccine provides any protection. Pre-clinical studies also gather extensive information on product safety. Only a small percentage of the vaccines that make it to the pre-clinical development stage move forward to the next stage.

Clinical Trials

A clinical trial is a research study in humans used to answer a question about an experimental drug, vaccine or other medical intervention. Clinical trials are conducted in sequential steps or "phases," each answering a different question. Small Phase I safety trials of AIDS vaccines ask: Is the vaccine safe in a small group of HIV-uninfected people who have undergone an extensive health screening process? Phase I trials may also look at vaccine immunogenicity. Phase II AIDS vaccine trials ask: Is this vaccine safe and immunogenic in a group of hundreds of HIV-uninfected people, who are known to be generally healthy?; and What is the best dose, dosing schedule, and route of immunization for the vaccine? Phase III AIDS vaccine "efficacy" trials usually enroll thousands of volunteers to ask: Does this vaccine provide protection against HIV infection, or reduce the severity of illness in people who receive the vaccine and later become infected with HIV through high-risk contact? If a Phase III trial shows that a candidate has either benefit then it may advance to the licensing and approval stage. The trial sequence may sometimes include large Phase IV trials after licensure.

Licensing and Approval

If a Phase III vaccine trial shows that the candidate has positive effects, then vaccine developers may submit an application to regulatory agencies for licensure. In the US the regulatory agency is the Food and Drug Administration; in the European Union it is the European Agency for the Evaluation of Medicinal Products; in South Africa it is the Medicines Control Council.

Regulators review everything about a product: all of the details of the manufacturing process, what it is made of, the benefits and risks of use, and the label and packaging that will be used to inform the public about the product. It is their task to determine whether the product is safe and of sufficient benefit to be made available to the public.

Several factors could influence decisions about whether to license AIDS vaccines. These include the level of benefit or efficacy observed in the Phase III trial, and the type of population that was enrolled in the trial. Some regulatory agencies may require a second "confirmatory" Phase III trial that may test the product in a different population, perhaps in a different age range or different part of the world.

Policy makers and health advocates are now working to develop and strengthen expertise in the regulatory agencies in the developing nations and to identify strategies for rapid licensing and approval processes.

Manufacturing and Delivery

Once an effective vaccine has been developed, it must be made in sufficient quantities to meet the global need. These supplies can only be made in large-scale manufacturing facilities which are costly and time-consuming to build. This is why vaccine developers begin planning manufacturing facilities long before they have a licensed product and even before they have results from a Phase III trial.

It is also essential to have systems and strategies to deliver the vaccines to people who need them. These systems require storage facilities and equipment and trained personnel who can safely administer the vaccine. The strategies include outreach and education campaigns to explain to people how the vaccine works, who should use it, and why the vaccine should not replace condoms or other strategies to avoid HIV, since all of these strategies must be used together.

Adapted from the December 2003-March 2004 Uganda AIDS Vaccine Update*, the newsletter of the Uganda Virus Research Institute-IAVI HIV Vaccine Program. For more information or a copy of the newsletter: www.iavi.org/uganda*