

# I A V I R E P O R T

A Newsletter on International AIDS Vaccine Research

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## INSIDE THIS ISSUE

### Why an HIV Vaccine is Scientifically Possible

*IAVI's scientific director makes the case for why an HIV vaccine is feasible.*

-1-

### A View from Uganda

*Dr. Edward Mbidde, one of Uganda's leading researchers, discusses AIDS vaccines developments.*

-3-

### Progress On AIDS Vaccines

*A closer look at a number of HIV vaccines currently in development and their future prospects.*

-4-

### Industry Perspective

*Dr. Stanley Plotkin, the scientific director of Pasteur-Merieux-Connaught, discusses AIDS vaccine development.*

-6-

### IAVI Launched

*Why the International AIDS Vaccine Initiative (IAVI) was formed and its priorities for the future*

-7-

### Community Leaders Advise IAVI

*Community leaders from developing countries meet with IAVI officials.*

-9-

### The Global Spread of HIV

-12-

## Why an HIV Vaccine is Scientifically Possible

by Margaret Johnston, Ph.D.

More than 12 years after HIV was identified as the causative agent for AIDS, enormous challenges remain in the effort to develop a safe and effective HIV vaccine. At this point, not a single candidate vaccine has progressed beyond phase II trials. Some even suggest that the goal of developing an HIV vaccine is unattainable.

Yet, a close look at recent scientific advances — both in understanding the pathogenesis of AIDS and in testing experimental HIV/SIV vaccines — suggests that the development of an AIDS vaccine is feasible. In fact, many researchers now believe that, with the proper investment of global resources and leadership, a vaccine for HIV is indeed possible.

The scientific rationale for supporting this claim includes the following:

### 1. Vaccines are effective against many viral diseases.

Vaccines work by stimulating specific immunological memory against an infectious agent such as a virus. Successful vaccination enables an individual to mount a rapid and potent immune response when exposed to a particular virus. This increased immune response holds the virus in check and prevents all signs of disease. A successful HIV vaccine will either prevent HIV infection or prevent disease by considerably limiting HIV replication.

*continued on page 2*

## WHAT IS THE INTERNATIONAL AIDS VACCINE INITIATIVE (IAVI)?

The International AIDS Vaccine Initiative (IAVI) is a global initiative dedicated to quickening the pace of HIV vaccine research and development, so that a vaccine suitable for use throughout the world can become reality. It was created to focus the world's attention on the need for a vaccine, and based on the belief that development of an HIV vaccine is possible.

### IAVI'S ROLE IS:

- to support research and development activities through a highly targeted applied vaccine development effort that focuses on the gaps in current R&D; and
- to work with governments, private industry, funders, regulatory authorities, UNAIDS and others to create more favorable environments that will encourage increased investment in vaccine research and development.

IAVI was incorporated in 1996 with the help of the Rockefeller Foundation, the World Bank, UNAIDS, the Merieux Foundation and Until There's a Cure. This initiative was created following a series of three international meetings with scientists, industry representatives, financial experts, international philanthropists, policy makers and members of the HIV-infected community at which the need for — and potential to create — an effective HIV vaccine were explored (*for more details, see page 7*). ♦



## 2. Experimental vaccines have protected chimpanzees and macaques.

Several experimental vaccines have protected chimpanzees from HIV infection. If an HIV vaccine blocks infection in humans, as it has done in chimps, it will certainly prevent disease. At this point the use of chimpanzees in HIV vaccine studies is limited because these animals do not get AIDS from HIV infection. Researchers, however, recently reported a chimpanzee that appears to have developed AIDS 10 years after being injected with HIV.

Macaque monkeys, on the other hand, consistently develop a disease like AIDS following infection by the simian immune deficiency virus (SIV). Some SIV isolates cause disease within a few years of infection. Even against these highly virulent strains of SIV, successful vaccination with live-attenuated — or genetically weakened — SIV has been observed. This suggests that a candidate HIV vaccine that generates the same HIV type of immune responses as these live-attenuated SIV vaccines will protect humans.

## 3. The human immune system can, at times, control HIV.

Several areas of research have shown that humans, at times, have the immunological capacity to respond effectively to HIV infection. These include:

**Children born to HIV-infected mothers:** In a number of well-documented cases, children born to HIV-infected mothers have first tested positive and subsequently negative for HIV infection, demonstrating that recovery from HIV infection can occur. The immune responses associated with viral clearance in these newborns is under investigation.

**Exposed but uninfected:** Recent evidence has demonstrated that a small percentage of individuals who have been repeatedly exposed to HIV remain uninfected. However, some carry an HIV-specific cellular immune response (known as cytotoxic lymphocytes or CTLs) that is normally not produced without active infection, suggesting that these individuals may have been HIV-infected and able to

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**Recent scientific advances suggest that an effective AIDS vaccine is feasible.**

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**Acute HIV infection:** In the period right after HIV infection occurs, most individuals mount a vigorous immune response which substantially clears most HIV from the blood. This is usually followed by a long disease-free period. Thus, generating stronger, more rapid and diverse immune responses by vaccination may be able to block the spread of viral infection and disease.

**Long term nonprogressors:** Evidence is increasing that a small percentage of individuals infected with HIV remain healthy for long periods of time, while still harboring very low levels of HIV in their blood and lymph system. Although the exact factors that lead to long term non-progression have yet to be determined, these individuals have strong memory CTL responses, suggesting that such responses may contribute to long-term, healthy survival.

## 4. Adults infected with attenuated HIV remain healthy.

Researchers have recently identified HIV-infected individuals who harbor only attenuated — or weakened — strains of HIV. These individuals have remained healthy for more than 12 years, with very low or undetectable levels of HIV and healthy immune systems. At least one of these individuals was probably exposed to HIV multiple times, suggesting that initial infection with an attenuated strain may have protected against subsequent pathogenic strains. This may be parallel to the results seen in macaques immunized with a genetically attenuated strain of SIV.

Live-attenuated vaccines may not prove suitable for widespread use. Yet, overall,

clear their infection. Some current candidate vaccines can elicit CTLs that may prove effective in clearing HIV or reducing infection to a level that does not result in disease.

these results suggest that humans may respond to HIV antigens presented in an optimal manner with an immune response that protects against subsequent exposures.

## 5. Experimental vaccines have induced strong immune responses in humans.

Experimental vaccines have been able to elicit neutralizing antibodies, which, when measured against laboratory strains of HIV, approach levels seen during natural infection (antibodies are considered a humoral immune response). In addition, certain recombinant live vectors (harmless viruses that are genetically altered to carry one or more HIV genes) have produced cellular immune responses in a significant percentage of recipients. The presence of CTLs against core proteins may help protect against diverse strains of HIV.

In some studies, antibodies from individuals who were given a candidate vaccine failed to neutralize “primary isolates” of HIV (that is, virus obtained from people infected with HIV, as opposed to laboratory strains). Yet one recent study, using an assay believed to be more sensitive (because it does not stimulate the cells prior to exposure to the virus and make them more prone to infection), reported that antibodies taken from a majority of individuals given a candidate vaccine neutralized primary isolates of HIV.

## 6. Mucosal transmission of HIV appears to be relatively inefficient.

HIV usually enters the body through the mucosal surfaces. Yet, the likelihood of HIV transmission is, on average, very small for each encounter. This suggests that there are natural barriers to HIV infection that, if augmented by effective immune responses, could prove to be entirely successful in halting HIV disease. Further, newer vaccine designs have proven somewhat effective in eliciting HIV-specific neutralizing antibodies in vaginal secretions. In a recent animal study, an SIV vaccine injected directly into the lymph tissue protected a majority of macaques given a rectal challenge.

continued on page 11

# A View from Uganda: An Interview with Dr. Edward Mbidde

*Dr. Edward Mbidde, director of Uganda Cancer Institute, is one of Uganda's foremost AIDS researchers. He is also a primary care physician, chair of the research subcommittee of the Uganda National AIDS Committee and an international authority on HIV vaccine research.*

**IAVI REPORT: How would you describe the AIDS epidemic in Uganda at this time?**

MBIDDE: We did a national study in 1989 and estimated that approximately 1.5 million people were infected with HIV out of about 18 million people. Today the epidemic continues to spread. In the rural communities, if you follow 100 women between the ages of 15 and 24 over one year, seven of those women will become newly infected with HIV. If you follow 100 men ages 19-30 over one year, you will see about six to seven new infections. Despite warning messages about how HIV is transmitted and using condoms, we still see these new infections, which are catastrophic.

**IAVI REPORT: How is Uganda preparing for HIV vaccine studies?**

MBIDDE: Uganda has come a long way. A number of years ago, the World Health Organization (WHO) was looking for places where vaccine trials could be initiated. They visited about 14 countries in Africa, Latin America and Asia and looked at what was necessary — a positive commitment, willingness of people to participate in vaccine trials, infrastructure, availability of cohort studies and the presence of new infections, which allows us to answer questions pretty quickly. Uganda, Brazil, Thailand, and Rwanda were selected as the four countries. Unfortunately, the war in Rwanda disrupted things there.

Since that time, Uganda has been preparing for the vaccine trials. We have cohorts of both men and women, in rural as well as urban centers. We have done several studies to see whether people will accept the vaccine trials. The acceptability rate has been high, ranging from 70 to 90 percent. And the government continues to commit itself to preventive vaccines. At the last vaccine conference, sponsored by the United States National Institute of Allergy and Infectious Diseases (NIAID), our minister of health reiterated Uganda's commitment to vaccine studies.

**IAVI REPORT: Do you have any timetable for going into clinical trials?**

MBIDDE: The timetable depends upon the availability of a product. We are putting together a proposal with the NIAID and Pasteur-Merieux-Connaught in France to test one of their products, most likely the ALVAC vaccine with the gp120 boost. This appears to be a safe and well-designed construct (see page 4).

**IAVI REPORT: Would the vaccine be based on a different strain of HIV than the present product?**

MBIDDE: At the moment, it's going to be based on HIV subtype B. We want to see whether this vaccine, which uses these conserved genes, would be able to elicit broad antibodies and cytotoxic T lymphocytes. The two of these responses, combined together, might prevent infection and, even if infection takes place, prevent disease. So we are hoping to start a phase I study by October. We'll look at safety; although it has been used in fairly big numbers in the United States and France. And we will look at whether we can elicit immunogenicity in this population in a trial of about 50 participants.

**IAVI REPORT: How can we encourage development of vaccines designed for the developing world where so much of the epidemic is occurring.**

MBIDDE: I can sum up by saying: we need a concerted global effort. We need people who have a vision beyond their borders.

While the developing countries may not seem to have resources to buy an effective vaccine, the need for the vaccine is certainly there, and the people will do everything possible to get that money available. We must examine what the impediments are for vaccine manufacturers. Many manufacturers say, "this business is too risky, we won't get involved." And they say, "even if we take the risk, who is going to buy these vaccines?" We need to look at ways vaccine developers can produce vaccines that will be effective against all the strains of HIV and still make a profit.

The developing countries are having a lot of problems. This disease is killing younger people, who are our future. These countries are agriculturally-based, so they need human beings to do the work. And these countries keep borrowing money to improve agricultural output. But without the human resources to operate the machinery, our funds are not going to good use. So we need, if necessary, to borrow money to support a vaccine.

I was looking at the history of the development of the smallpox vaccine. What is interesting is that about (U.S.)\$150 million was necessary to develop the vaccine and implement the programs to

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# PROGRESS IN AIDS VACCINE DEVELOPMENT

by David Gold

At first glance, prospects for rapid advances in the development of an AIDS vaccine appear bleak. Only a limited number of approaches are being actively pursued, most of them based on a subtype of HIV found in less than 10 percent of the world's AIDS cases. Few experimental vaccines appear ready to move into large human studies. With a few notable exceptions, the leading pharmaceutical and biotechnology companies have steered clear of major investments in the field. Asked recently about the state of AIDS vaccines in development, Dani Bolognesi, a leading U.S. researcher, observed that "the pipeline is almost shut down."

Despite these critical gaps, many observers remain hopeful, and real advances continue to be made on a number of products. Below is a brief review of the progress being made in four widely followed approaches to AIDS vaccine development.

## LIVE-VECTORED VACCINES

**BACKGROUND:** The product that has shown the most promising immune responses in humans is a combination of a vaccine known as ALVAC and a booster shot of a gp120 vaccine. The ALVAC vaccine, which is manufactured by the French pharmaceutical company Pasteur-Merieux-Connaught (PMC), consists of HIV genes inserted into a live canary pox virus (which is harmless to humans).

The gp120 vaccine, manufactured by Chiron/Biocrine (Chiron), a U.S.-based biotechnology venture, is based on the envelope protein of HIV (known as glycoprotein120). It is hoped that the canary pox vector generates an immune reaction — known as a cellular immune response — which researchers increasingly believe is critical to protecting against HIV infection. The

gp120 booster, researchers believe, will induce a strong antibody response.

The first ALVAC product, vCP125, consists of gp160 spliced into the canary pox vector. A second generation ALVAC, vCP205, contains a number of HIV genes (envelope, gag and protease) inserted into the canary pox vector. The third ALVAC product, vCP300, contains additional HIV genes (including nef) to elicit an even broader response.

### CLINICAL STUDIES:

Preliminary studies in the United States and France suggest that the first two ALVAC products are safe and can induce some cellular and antibody response in humans. Data from early studies using lower doses of vCP205 show that 25 to 50 percent of participants had new cellular responses to HIV. Higher doses of the vaccines appear to generate greater cellular responses.

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) is working with PMC to identify the level of immune responses required to move ahead to a large phase III efficacy study. In the meantime, phase II studies should start next year, with phase III efficacy studies possibly beginning in 1998.

**INTERNATIONAL STUDIES:** All ALVAC products currently in human trials are based on HIV subtype B, the predominate subtype in North America and Europe. PMC is developing ALVAC vaccines based on other subtypes, but there are no definitive plans for trials of these products.

Phase I studies of the ALVAC vaccines (based on HIV subtype B) could start later this year in both Uganda and Thailand. These studies will examine what type of cellular immune responses the vaccines

can generate in individuals with non-subtype B HIV.

**OUTLOOK:** At this time, the ALVAC vaccine with the gp120 boost appears to

be the best bet of any candidate vaccine to go into phase III efficacy studies. Most observers believe that efficacy trials will go ahead in the United States unless some unanticipated results emerge from the phase II studies. In the meantime, many hope that Pasteur-Merieux will move quickly to develop ALVAC vaccines based on subtypes of

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*The ALVAC vaccine with a gp120 boost appears to be the best bet to go into phase III efficacy trials.*

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HIV found in the developing world.

## GP120 VACCINES

**BACKGROUND:** The two most widely tested HIV gp120 vaccines have been developed by Chiron, and another U.S.-based biotechnology company, Genentech. Both products have been studied extensively in phase I and phase II studies.

In June 1994, the NIAID decided not to proceed with a large-scale efficacy study of these vaccines in the United States. Supporters of the decision argued that the vaccines did not generate antibodies that could neutralize primary isolates (virus obtained from people infected with HIV as opposed to laboratory strains.) Those opposed to the decision pointed to the fact that the gp120 vaccines had protected a number of chimpanzees from infection with HIV.

Earlier this year, Genentech announced that it was creating a new company, Genenvax, to bring its gp120 vaccine to market. The parent company will provide \$2 million in start-up costs and an additional \$18 million will be sought in private financing for large clinical trials and new vaccine formulations.

**CLINICAL STUDIES:** The gp120 vaccines have been widely studied in humans and appear to be quite safe and capable of creating significant antibody response. Cellular immune responses, on the other hand, appear far weaker.

**INTERNATIONAL STUDIES:** In October 1994, after the United States' decision not to proceed with phase III trials, the World Health Organization (WHO) agreed that efficacy trials of gp120 vaccines could be undertaken in other countries where appropriate. WHO cited the desperate situation that AIDS was causing in many countries and the fact that vaccine efficacy studies would need fewer participants due to higher rates of new infections in these countries.

While these studies have not yet taken place, phase I studies of Chiron's and Genentech's gp120 products are underway in Thailand. Both are based on the subtype B strain, found in industrialized countries and in some parts of Thailand. Chiron is developing gp120 vaccines based on HIV subtype E (predominant in Thailand) and a bivalent vaccine based on both the E and B subtypes. Phase I studies of these products are scheduled to begin sometime in 1996 in Thailand. Genenvax, if it can raise the necessary funds, plans to test its gp120 vaccine (subtype B) in the United States and a subtype E version in Thailand sometime in 1997.

**OUTLOOK:** The primary weakness of gp120 products, as single agents, remains their apparent inability to elicit certain cellular immune responses. Yet, many believe that future studies of gp120 can yield important information about designing an effective HIV vaccine. Efforts to develop subtype E gp120 vaccines are particularly important, both scientifically and as an example of one industry's commitment to design HIV vaccines for the developing world.

*Impressive results in animals have encouraged companies to expand their HIV-DNA vaccine programs.*

## DNA VACCINES

**BACKGROUND:** Researchers are increasingly hopeful about a class of vaccines known as DNA vaccines. These vaccines, which are being studied for many diseases, including HIV, influenza, tuberculosis and malaria, work by injecting genetic material of the organism directly into the body. The genetic material —

or fragments of DNA — encodes information and gets the individual's own cells, in effect, to make the vaccine. The scientific appeal of this approach is that it attempts to create the immunogenicity of a live vaccine without using a live virus.

Animal studies suggest that DNA vaccines are quite immunogenic, particularly in generating cellular immune responses. In addition, they are easy and inexpensive to manufacture.

According to Dr. Norman Letvin of Harvard University School of Medicine in the United States, the manufacturing process for DNA vaccines "is quite simple, in fact trivial." He believes that HIV-DNA vaccines are one of the few approaches with the potential to be distributed throughout the world at a reasonable cost.

To date, DNA vaccines have shown impressive results in animals. Studies by Merck, the U.S.-based pharmaceutical giant, demonstrated that a DNA vaccine can prevent influenza in animals. Research on mice and monkeys by Agracetus, a U.S.-based biotechnology company and Chiron suggest that an HIV-DNA vaccine with a gp120 booster to stimulate antibody response is feasible.

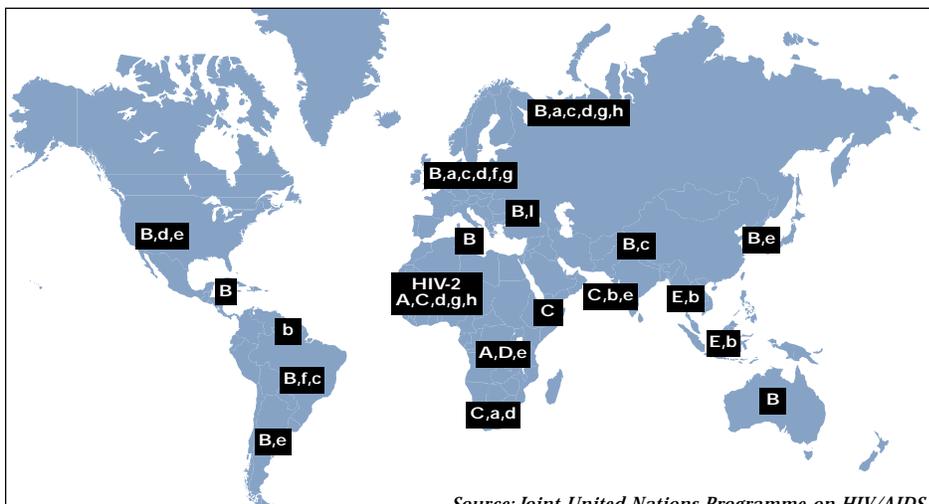
Scientists working with Apollon, another U.S.-based biotechnology company, report that the company's HIV-DNA vaccine has generated strong immune responses that appear to protect chimpanzees against HIV.

This promising animal data encouraged a number of companies to expand their DNA vaccine programs. Merck's DNA influenza vaccine is currently in human trials while its HIV-DNA vaccine is in active development.

Apollon is studying a DNA vaccine for herpes, human papilloma virus and T-cell lymphoma. Auragen is developing a "DNA gun" which takes a much smaller amount of DNA covering what is described as microscopic "gold balls" and, in effect, shoots it into the skin. Pasteur-Merieux-Connaught's DNA program includes vaccines for HIV, Lyme disease and malaria.

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## GLOBAL BREAKDOWN OF HIV SUBTYPES



*Source: Joint United Nations Programme on HIV/AIDS*

**A-I:** HIV genetic subtypes of **high prevalence** in a region  
**a-i:** HIV genetic subtypes of **low prevalence** in a region

# Industry Perspective: An Interview with Dr. Stanley Plotkin

*Dr. Stanley Plotkin, an influential figure in AIDS vaccine development, is the medical and scientific director for Pasteur-Merieux-Connaught (PMC), a Paris-based pharmaceutical company.*

**IAVI REPORT: Can you describe the HIV vaccine programs at Pasteur-Merieux-Connaught (PMC)?**

PLOTKIN: We have developed four experimental HIV vaccine programs. The first is an envelope glycoprotein (gp120) program. The second is a peptide program based on a number of complicated HIV peptides we have created. The third is the so-called pseudovirion vaccines, in which we essentially construct a virus particle that is non-infectious but contains most of the viral structural proteins so that it is immunogenic. And the fourth is a recombinant vaccine called ALVAC that is based on canary pox, a virus of canary birds which is harmless to humans, and into which you insert genes of pathogenic agents such as HIV. The regimen that seems most interesting is a regimen that starts with canary pox and recombinant and then follows with the gp120 boost, produced by Chiron. Using both of these, we see neutralizing antibodies and good cellular response.

**IAVI REPORT: Could you describe the plans for the phase III studies?**

PLOTKIN: If the phase II studies go well over the next 18 months, we'll sit down with the National Institute of Allergy and Infectious Diseases, the U.S.A. (NIAID) and they'll decide whether to organize an efficacy trial, which is planned for 1998.

**IAVI REPORT: Are there any international trials planned other than in the United States and France?**

PLOTKIN: We are planning small phase I trials of the ALVAC product in Uganda and Thailand. Since the vaccine is based on subtype B (found in North America and Europe), we would like to see what type of cellular and antibody immune responses we get. These will be small trials.

**IAVI REPORT: Is PMC developing any vaccines based on HIV subtypes found in the developing world?**

PLOTKIN: We are currently creating ALVAC vaccines based on three different HIV subtypes. These need to be studied and tested for safety. But the fact is that a vaccine has got to make it in the developed world before it's made in the developing world. That's just the realities of things. These are heavy investments.

There is also a more important scientific reason. Our knowledge of the subtype B viruses is much greater than the other subtypes. And the population in which we can do our initial tests are populations where subtype B is found. If we were to start studies in the developing countries instead of France and the United States, people would claim we are being unethical.

So we are progressing in a reasonable way by demonstrating the principle on the subtype B strains and then going to developing countries to see if the principle applies there. If things work well, we would certainly expand in the developing world. But you cannot do everything at once. If you rush too fast, you're going to trip and it will be bad in the long run.

**IAVI REPORT: Will Chiron's gp120-subtype E be used in some ALVAC studies?**

PLOTKIN: We are working closely with Chiron on the ALVAC plus gp120 boost approach. We have an agreement to collaborate scientifically to find out whether this concept works. It is very important that two major companies are working together to try to develop a useful vaccine regimen.

**IAVI REPORT: What are the real roadblocks to industry investment in HIV vaccines?**

PLOTKIN: The real roadblock is pessimism about whether vaccines are going to work. It is not because companies aren't interested or any other paranoid reason. It is simply that they have not been very optimistic and consequently are reluctant to get involved.

**IAVI REPORT: Why do you think so few major companies are investing in HIV vaccines?**

PLOTKIN: It's really been the lack of good ideas. Now with the advent of the DNA vaccines, companies are coming back in.

**IAVI REPORT: Is PMC interested in HIV-DNA vaccines?**

PLOTKIN: Yes. It appears to be a terrific approach. But the clinical experiments have just started. If the clinical results are as good as they are in animals, then we really have something. But I'm not going to predict.

**IAVI REPORT: What is the best case timeline for the HIV-DNA vaccines?**

PLOTKIN: When it all started I would have said about 10 years until large efficacy studies. But we're more optimistic now. For a disease

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*The real  
roadblock  
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like AIDS, where the risk/benefit ratio is so clear, conceivably, it could be five years to licensing, but that's if everything really goes swimmingly. If phase I trials go well, then there's going to be tremendous justification for pushing into phase II and phase III. But, again, that is the very best case scenario.

**IAVI REPORT: If the ALVAC vaccines show efficacy, how do we provide them to the developing world and who pays?**

PLOTKIN: I wish I had a good answer for that. It's the same for every other vaccine. In many countries, the vaccine is bought by UNICEF or by rich country donors. In other cases, the countries themselves decide that the vaccine is worth spending money on. The keystone of the system is that the research costs are recouped in North America and Europe and the vaccines are sold in the developing world at much, much lower margins. The system has not worked terrifically well but, on the other hand, it hasn't worked terrifically badly either. And the relatively high rate of childhood vaccination seen lately in most parts of the world is the result of that system.

**IAVI REPORT: How much is PMC spending on AIDS vaccine development?**

PLOTKIN: AIDS vaccines are the number one research and development program here, constituting 20 percent of our total R&D budget. And we receive support from the French government, so in fact, it's more than 20 percent.

**IAVI REPORT: What explains this commitment when so many other companies are avoiding AIDS vaccine development?**

PLOTKIN: PMC believes this is a very important scientific problem. The company has historically been interested in diseases of global importance. I'm not going to say that we don't expect to make money in this area, although some think we never will, given the high rate of failure.

**IAVI REPORT: Where do you see the International AIDS Vaccine Initiative (IAVI) fitting into the picture?**

PLOTKIN: IAVI can play an important role in mobilizing the diverse groups around the world in AIDS vaccine development. It can also address gaps in the existing research effort and questions as to how to distribute AIDS vaccines to the developing world. This is an extremely worthwhile effort.

*continued on page 12*

# INTERNATIONAL AIDS VACCINE INITIATIVE LAUNCHED

by David FitzSimons

*[Editor's note: This story is excerpted, with the author's permission, from a larger story which appeared in The AIDS Newsletter (April 1996), a UK-based newsletter on AIDS/HIV-related research published by the Centre for Agriculture and Biosciences International.]*

## BACKGROUND

Well into the second decade of the HIV epidemic, the virus continues to spread virtually unchecked throughout the world. Over the next five years, more than 18 million people worldwide — an average of about 7,500 people a day — will be infected with HIV. More than 90 percent of these infections will be in developing countries. While it is estimated that at least (U.S.) \$1.5 billion worldwide was spent on HIV prevention (1993), most of this was spent in the industrialized world. And according to researchers, even with an immediate 15-fold increase in worldwide

HIV prevention spending, the number of new infections would be reduced by no more than 50 percent. These expenditures would need to be continued indefinitely.

This grim reality has led many to believe that development of a safe, effective, and inexpensive HIV vaccine is the only way to stem the epidemic. Vaccines have halted the spread of many infectious diseases including smallpox, polio and, in many countries, measles.

Many questions still remain about HIV and how the immune system functions. Nevertheless, there are some encouraging signs that a vaccine is possible.

Yet, experts suggest that prospects for an HIV vaccine are limited by lack of investment in the area, particularly in the private sector. Several biotechnology companies have withdrawn from the field and AIDS vaccines appear to have lost their appeal on Wall Street. The result: little new money is being invested. While more than

\$5 billion was spent on HIV-related health care in 1993, less than \$160 million (including public and private sectors) was invested in worldwide HIV vaccine research and development.

## ROCKEFELLER FOUNDATION POLICY MEETINGS

Against this backdrop, the Rockefeller Foundation of New York convened a series of three international meetings in 1994 and 1995 to bring together scientists, public health officials, development specialists, financial experts, industry representatives and members of the HIV and philanthropic communities to examine these issues.

The first meeting was held in Bellagio, Italy, in March 1994. Participants concluded that HIV vaccine development efforts by pharmaceutical and biotechnology companies was extremely limited. Moreover, incentives for industry to invest in the field were almost non-existent. In addition, vaccines that were being developed were based solely on HIV subtypes found in North America and Europe, whereas the vast majority of new

*continued on page 8*

## **IAVI Launched continued from page 7**

infections were occurring in developing countries.

Participants concluded that a new global initiative should be established with the mandate of accelerating the development of HIV vaccines appropriate for worldwide use. The initiative, it was suggested, would focus on reducing the obstacles to vaccine development and filling the gaps in the current effort. The establishment of a small funding secretariat to run the initiative was recommended.

### **SCIENTIFIC BARRIERS**

In October 1994, a second meeting of 15 distinguished scientists met in Paris to discuss scientific barriers to the development of preventive HIV vaccines. The participants identified seven principal conclusions that shaped the scientific agenda:

- Development of less risky peptide, subunit and vectored vaccine products should be continued. Because they may be only partially effective, global efforts on other approaches should be intensified.
- The success of a live-attenuated approach in the SIV/monkey model suggests that a greater effort be put into developing vaccines based on complex antigens and whole killed virus.
- Because no ideal animal model for HIV disease currently exists and the markers of protection are not certain, trials must be done in at-risk human populations to obtain clear evidence of success or failure of particular vaccines.
- Researchers and officials from developing countries must be full partners in the planning and execution of all stages of vaccine research and development.
- Candidate vaccines should be designed for several HIV subtypes and would ideally match the subtype prevalent where the trials are performed.
- There must be a strong emphasis on safety testing before and during human trials.
- Since incentives are lacking for industry to develop vaccines perceived as less safe or designed for developing countries, the new initiative must take on this mission.

### **FOCUS OF THE INITIATIVE**

The latest meeting was held in August 1995 in New York, gathering individuals from industry, international finance, law, and the public health sectors to discuss the financial and structural issues relating to the initiative. Participants proposed that the focus of the initiative be to support targeted research and development activities (focusing on gaps in current efforts and the needs of developing countries) and to create a more enabling environment for HIV vaccine development.

### **IAVI LAUNCHED**

In January 1996, the International AIDS Vaccine Initiative (IAVI) was incorporated. For the time being the secretariat of IAVI is being housed at the Rockefeller Foundation in New York. An interim board of directors has been formed, with members Dr. Peter Piot, executive director of the Joint UN Programme on HIV/AIDS; Dr. Philip Russell, president, Albert Sabin Vaccine Foundation and professor, Johns Hopkins University, as well as former adviser to the Children's Vaccine Initiative; and Dr. Seth Berkley, associate director of Health Sciences at the Rockefeller Foundation. Margaret Johnston, Ph.D., formerly deputy director of the division of AIDS for the U.S. National Institute of Allergy and Infectious Diseases, has been appointed as the scientific director of IAVI. A worldwide call for nominations for the chief executive officer has been issued.

The initiative's first priority is to launch a directed vaccine research and development program, led by Johnston and a scientific advisory committee made up of some of the world's leading scientists working in AIDS vaccine research and related fields.

This program will support promising research efforts that are currently under-explored. A secondary priority is to undertake a series of activities aimed at reducing key uncertainties and risks associated with private industry investment in AIDS vaccine development.

### **CONCLUSION**

The need for an HIV vaccine continues to grow more critical as the epidemic spreads and the burden of illness and disease lies increasingly on the developing world. The irrelevance of currently priced combination antiviral therapy for the vast majority of infected people in the world reinforces that need.

The International AIDS Vaccine Initiative is well placed to catch this tide, especially if it can bring together the private and public sectors in coordinated global efforts. Considerable scientific, commercial and social barriers to the development of an effective vaccine remain in place. But, the promise of coordination in developing more varied vaccine approaches and the likelihood of seeing successful results applied on the basis of worldwide need, ought to persuade both the private and the public sectors, and one hopes additional philanthropic institutions, to participate in and support this initiative. ♦

*David FitzSimons is the editor of The AIDS Newsletter.*

## **IAVI SCIENTIFIC COMMITTEE TO BE ANNOUNCED**

This summer, IAVI will announce the selection of a worldwide scientific advisory committee that will chart the initiative's scientific program and recommend priority areas for support. According to IAVI's Scientific Director Margaret Johnston, Ph.D., who oversees the international search, the committee should be finalized within the next month and will hold its first meeting this summer.

Johnston reports that many of the world's leading scientists in AIDS vaccine research and related fields have expressed interest in serving on the committee. Between February and April of this year researchers nominated more than 200 scientists from approximately 30 countries for the scientific advisory committee. A nominating committee has met to review nominations and submit recommendations to IAVI's board of directors.

Johnston is particularly pleased with the high quality of scientists and the geographical breadth that will be represented on the committee. "Most important," she noted, "is that we will bring together experts in HIV/AIDS and vaccine development from both industrialized and developing countries to help guide the scientific program."

# Community Leaders from Developing Countries Advise IAVI

Representatives from developing countries in Africa, Asia and Latin America met in New York City on May 16-17, 1996, to discuss worldwide efforts to develop an HIV vaccine. Sponsored by the International AIDS Vaccine Initiative (IAVI), the meeting included discussions about the devastating impact HIV was having in the developing world.

Eka Esu Williams, an AIDS prevention worker in Lagos, Nigeria, reported that in her country two million people are now believed to be infected with HIV. The epidemic, she noted, is increasingly driving itself into the younger populations.

In India, a similar pattern is emerging. Studies by the World Health Organization (WHO) suggest that in five years, India will likely have more cases of AIDS than any country in the world. According to Vimla Nadkarni of the Tata Institute of Social Sciences in Bombay, India, "AIDS is spreading in pandemic proportions in my country."

Many of the representatives noted that women in developing countries are being particularly hard hit by AIDS. Jorge Beloqui, an AIDS activist from Sao Paulo, Brazil, reported that in his city AIDS is now the leading cause of death among women ages 20-45.

## PREVENTION NOT STOPPING EPIDEMIC

The participants agreed that current prevention efforts are unlikely to stop the epidemic. The huge social and economic challenges facing developing countries make broad-based behavioral interventions extremely difficult. Noerine Kaleeba of the Joint UN Programme on HIV/AIDS (UNAIDS) told the gathering that "in the last 15 years, we in Uganda have expanded every energy we have in behavioral interventions, but the devastation from AIDS continues, every day."

Deteriorating social conditions continue to spread HIV. In Nigeria, according to Williams, "interventions are a huge challenge. The social and economic environment does not support people making changes and a majority of people live in hard-to-reach rural areas."

"Behavioral interventions are important," noted Beloqui, "but require a great deal of money. An AIDS vaccine is the only way poor people from my country will be protected."

## GLOBAL INITIATIVE SUPPORTED

IAVI officials discussed the initiative's efforts to focus attention and resources on HIV vaccine development. Dr. Seth Berkley, chairman of the interim board of directors of IAVI and associate director of health sciences at the Rockefeller Foundation, gave an overview of IAVI and its plans for the future. Margaret Johnston, IAVI's scientific director, presented the initiative's research agenda.

- Participants voiced support for IAVI's efforts to develop HIV vaccines that can be used in all parts of the world. "IAVI is important," Nadkarni said, "because it is looking at the issue on a global level and focusing on countries that need the vaccine. A lot of very enlightened and knowledgeable people on an international level are getting involved in this process."
- Many believe that the initiative can attract critical new support for the vaccine effort. "IAVI can draw many people from different walks of life, fill in the gaps and provide a sense of urgency about developing an HIV vaccine," noted Kaleeba.
- There was much discussion about the limited resources currently being invested in vaccine development. According to Beloqui, "it is very important to have an initiative that can stimulate research on AIDS vaccines. New approaches and products are desperately needed."

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***"An AIDS vaccine is the only way poor people from my country will be protected."***

**—Jorge Beloqui, AIDS activist, Sao Paulo, Brazil**

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## CONCERNS VOICED

While participants voiced strong support for the initiative, they expressed a number of concerns about overall HIV vaccine development. Researchers were urged to clearly acknowledge past mistakes in vaccine trials and to set strict ethical standards for new trials. The leaders suggested that particular attention be given to stimulating and supporting in-country solutions for the diverse issues inherent in testing vaccines. They emphasized that transparency, openness and systematic sharing of information with a variety of constituencies should be guiding principles for vaccine research.

Nadkarni clearly expressed the sentiment of the group by calling for "greater collaboration from the beginning. Researchers cannot come in as outsiders and try to force something on people."

IAVI's Scientific Director Johnston strongly agreed, noting that "information concerning HIV vaccine research and development must not be the sole property of scientists. This information must be distributed to and understood by communities, so that they can fully participate in the development process."

## PLEDGE TO MOVE FORWARD TOGETHER

At the end of the two days, Berkley was enthusiastic. "It was very exciting to have representatives from 14 diverse countries around the world start out with quite different approaches, ideas and perspectives and, by the end of the meeting, coalesce around the need for an AIDS vaccine." The participants, he added, "came up with many useful ideas on how IAVI can move forward and get communities involved."

Johnston and Berkley noted that prior to this meeting, IAVI officials met with AIDS activists from New York, San Francisco, Washington and Europe.

*continued on page 10*

**PERSPECTIVE FROM UGANDA** *continued from page 3*

eradicate smallpox. Most of this money came from developing countries because they had the burden of the disease. So the developing countries need to put their resources together and say to the vaccine developers, "Look, we are able to buy your product when it becomes available." Furthermore, people must remember that HIV can spread beyond the borders. The strains that we have here in Uganda, in Africa, in Asia, could easily find their way to the United States, Europe and Australia.

**IAVI REPORT: How do we increase investment in new AIDS vaccine products?**

MBIDDE: The biggest problem is the slow pace at which we're moving in human studies. We need to accelerate experiments in animals. But if we don't perform studies in humans, we may not learn as much as we could. We need to examine how to best utilize human studies to overcome some of the areas we don't understand.

For example, we don't know all the correlates of immunity (the immune reactions needed for a vaccine to protect). But there have been very successful vaccines developed where people did not know the correlates of immunity. So the bottom line is that we need to move from animal experiments to human trials that will give us useful information on various vaccine products and approaches.

**IAVI REPORT: What kind of role do you see for an initiative such as IAVI?**

MBIDDE: The beauty of IAVI is that it can have a vision in all directions. In other words, it is not being pushed by the agenda of any one group. It is not committed just to the policy makers, or to the vaccine developers, or to consumers. Because of this, IAVI has the ability to bring all three groups together — the manufacturers, the policy makers, and the consumers — so that they can put together the best program to accelerate vaccine development.

For example, one country, believing that HIV is a huge problem, may want to consider a study of a candidate vaccine that may be quite effective, but also more risky, such as the live-attenuated vaccine developed by Ronald Desrosier. Now, IAVI can play a very central role in bringing together the researchers, an industry sponsor and health officials from the country to develop and possibly test the product. The initiative can also let the manufacturers know that developing countries, the ultimate consumers of these vaccines, want to do everything possible to work together with industry to insure that appropriate vaccines are developed. In a real sense, IAVI can help bring industry and consumers together in this effort.

**IAVI REPORT: Tell us a little bit about your own work.**

MBIDDE: My background has been as a physician in oncology at the Uganda Cancer Institute. In the 80s, we began doing research in AIDS, because it overlaps with oncology. We studied the role of HIV in cancer in Uganda and also looked at factors responsible for heterosexual transmission of HIV.

In our work we also provide people with information and education. That has made a dent in the epidemic. But unfortunately, given our resources, behavioral interventions cannot be very effective. So, I have become much more convinced that we need to aggressively study vaccines. I'm getting more involved as an advocate for vaccine trials and also in evaluating vaccines themselves.

**IAVI REPORT: Why do you think it has taken so long to develop real international coordination in the area of HIV vaccines?**

MBIDDE: When the epidemic started, there were a great deal of accusations. People thought AIDS was their neighbor's problem. Now they have begun to see that the epidemic is not a specific country's epidemic. It moves on, and probably moves back and forth.

To be able to fight it effectively, we need a concerted global effort. And in that effort, each of us will have to bring something to bear. The industrialized countries will bring the technology and the products. The developing countries have not been able to invest much funds, but we must be part of the effort and give what we can. So given the fact that we bear the brunt of the epidemic, what can we offer? We can offer sites where answers can be obtained pretty fast. But we will

not allow ourselves to be used. We are part and parcel of the entire effort and we will sit together with international community, side by side, in working to develop a safe and effective HIV vaccine. ◆

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***The bottom line is that we need to move more rapidly from animal experiments to human trials that will give us useful information.***

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**COMMUNITY LEADERS** *continued from page 9*

Those meetings also gave community leaders an introduction to IAVI and allowed for broad discussions about HIV vaccine development.

One of the most critical issues that came out of the meeting, according to Berkley, is the huge — and growing — disparity that exists between developed and less developed countries in the AIDS epidemic. As promising therapies rapidly become available in the United States and Europe, the developing world is being left even farther behind in dealing with the epidemic.

Participants also found it useful to share their perspectives with other community leaders from around the world. "Meeting people from other developing countries where vaccine trial sites are being prepared," noted Beloqui, "was helpful and exciting. This meeting will help us prepare a network around these issues." ◆

## 7. Vaccines that lower viral load may have a public health benefit.

Several studies suggest that viral load levels play an important role in HIV transmission and disease progression. Studies of HIV-infected mothers and their newborns have demonstrated that the level of HIV in the mother is a good indicator of the likelihood of transmission to her child. In adults, the level of virus observed following seroconversion is a good general predictor of the time to development of AIDS. A vaccine that elicits immune responses that result in lower viral load levels following infection could have a substantial benefit. Additional studies are needed to better understand whether individuals with low viral levels of HIV might still be infectious.

Thus, recent scientific evidence in natural history and vaccine studies, both in humans and animals, suggest that a successful vaccine is technically possible. Despite the many uncertainties about how best to design a safe and effective HIV vaccine, it is now clear that a concerted worldwide effort can be successful. ◆

*Margaret Johnston, Ph.D., is the scientific director of the International AIDS Vaccine Initiative (IAVI) and was formerly deputy director of the division of AIDS for the National Institute of Allergy and Infectious Diseases, U.S.A.*

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### PROGRESS continued from page 5

**CLINICAL STUDIES:** Earlier this year, Apollon's DNA vaccine became the first HIV DNA vaccine to enter human trials. The product is being studied as a therapeutic vaccine in HIV-positive participants. No significant side effects have been seen. Recently, the company received approval by the U.S. Food and Drug Administration to begin a study of its DNA vaccine in HIV-negative volunteers. This study is currently enrolling participants.

**INTERNATIONAL STUDIES:** All HIV-DNA vaccines currently in development appear to be based on HIV subtype B. There are no current plans to begin trials of HIV-DNA vaccines in any developing countries.

**OUTLOOK:** DNA vaccines represent a promising approach to HIV vaccine development. The start of human studies of HIV-DNA vaccines is an important step forward. Smaller biotechnology companies, like Apollon and Auragen, are aggressively studying these vaccines. World-class vaccine companies like Merck, Pasteur-Merieux-Connaught and Chiron are also investing heavily in the field. But, there appears to be little evidence of plans by any company to study DNA vaccines based on HIV subtypes found in the developing world.

### LIVE-ATTENUATED VACCINES

**BACKGROUND:** In 1992, researchers from the lab of Ronald Desrosiers at the New England Primate Center (U.S.A.) demonstrated that a live attenuated vaccine made by deleting a gene of HIV known as *nef* protected monkeys against simian

immune deficiency virus (SIV). Researchers in the United Kingdom and France replicated these results. Desrosiers and colleagues then began trying to delete as many genes as possible from the live attenuated virus, while still preserving the vaccine's immunogenicity.

However, in 1995, it was reported that an SIV vaccine with three genes deleted caused an AIDS-like illness and death in newborn monkeys. Yet, researchers at the University of California at Davis in the United States, reported that a different attenuated SIV vaccine was safe in newborn monkeys.

Recently, researchers modified the *nef*-deleted vaccine by insertion of a gene for gamma interferon and were able to protect juvenile monkeys against SIV challenge. In addition, when the vaccine was given to newborn monkeys, it did not cause disease or death. In chimpanzees, a *nef*-deleted HIV vaccine has produced inconsistent results.

Development rights to the gene-deleted attenuated HIV vaccines are held by Therion, a U.S.-based biotechnology company.

However, the company does not appear to be actively pursuing this approach at the current time.

In Australia, researchers are trying to develop an attenuated vaccine based on sequences found in a cluster of HIV-infected individuals who received blood from a single donor over 10 years ago and remain healthy with no sign of disease or immune suppression.

**CLINICAL STUDIES:** At this time, due to safety concerns, no human studies are currently planned for any live-attenuated HIV vaccine.

**OUTLOOK:** In the SIV/monkey model, live-attenuated vaccines have demonstrated the most impressive and consistent protection of any vaccine. Still, some believe that, because of the potential risks involved, a live HIV vaccine is unlikely ever to be tested in humans. However, others suggest that if current products prove ineffective and the epidemic continues to devastate many parts of the world, researchers and public health officials will have to take a very serious look at human trials of live-attenuated HIV vaccines.

### CONCLUSION

A slight but real sense of optimism is beginning to emerge in the effort to develop an AIDS vaccine. Beyond the four classes of vaccines discussed above, a number of other approaches are currently being studied, including whole killed viruses, peptide-based vaccines and pseudovirions. But despite the best efforts of researchers, many fear that the critical gaps — in our knowledge of HIV and the immune system, in private industry's limited investment in the field and a lack of products designed for use in the developing world — will continue to hamper efforts to develop an AIDS vaccine. ◆

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# THE GLOBAL SPREAD OF HIV

According to the World Health Organization, by the year 2000, 30 million to 40 million people may be infected with HIV.

ESTIMATED DISTRIBUTION OF ADULT HIV INFECTIONS SINCE THE START OF THE PANDEMIC IN THE 1970s:



Source: Joint United Nations Programme on HIV/AIDS

## WORLDWIDE AIDS FACTS

- **By the year 2000**, the U.N. agency expects that 10 million people will have developed AIDS and more than 8 million will have died from the disease.
- **By the year 2000**, it is established that AIDS will cost the world (U.S.)\$514 billion.
- **Every day** more than 7,500 people are newly infected with HIV.
- **In sub-Saharan Africa**, north Africa and the Middle East, HIV infections have doubled since 1994; in south and southeast Asia, the increase was 70%.
- **More than half of all HIV infections** have been in people under age 25.
- **By 2000, 5 million to 10 million children** will be infected through their mothers.

STANLEY PLOTKIN *continued from page 7*

**IAVI REPORT: What about calls for more directed or targeted research efforts?**

PLOTKIN: My thoughts are somewhat ambivalent. There are clearly projects that would be useful. We need to analyze what needs to be done through the contract mechanism or other mechanisms and get people to do it. But it's not as if you could give \$100 million to somebody and they will make a vaccine.

What will attract companies into the field is a clinical result that gives hope that you can really protect against HIV. That will change things completely. So that first positive result is really what is needed.

· Certainly we could use more money. There are things that we need to do together that we're doing now in sequence because of limited resources. But we need more than just money. We need better ideas.

· **IAVI REPORT: If the ALVAC vaccines prove ineffective some fear that more companies will drop out of HIV vaccine development and there will be little else to study. Do you agree?**

· PLOTKIN: It will be a blow. Absolutely. But the DNA research is coming up rapidly. And several companies are still working on protein and peptide vaccines. They haven't dropped out. What we need to promote is the idea that an AIDS vaccine is important and just because of one or two failures, we shouldn't give up. ◆

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