

IAVI REPORT

A Newsletter on International AIDS Vaccine Research

Vol.3 No.3 July-September 1998

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HIV DNA Vaccines Move Slowly Into Human Trials

A number of companies are developing HIV DNA vaccines, but very few products have advanced into human trials

by David Gold and Sam Avrett

The central goal of an HIV vaccine is to induce a human immune response that can protect against chronic infection and/or disease. Evidence now indicates that the human immune system is most likely to prevent or control HIV infection through a combination of responses, including antibodies and cytotoxic T lymphocytes (CTLs). During the past 15 years, recombinant DNA technology has offered researchers several possibilities for innovative HIV vaccine designs, including recombinant proteins (such as gp120 or gp160), recombinant live vector vaccines (such as

canarypox vectors) and DNA vaccines. Live vector vaccines and DNA vaccines may hold special promise due to their ability, as shown in primates, to generate CTL responses.

HIV DNA vaccines, also known as "nucleic acid", "plasmid DNA" or "naked DNA" vaccines, consist of bacterial plasmids carrying genetic material that code for parts of the HIV virus. In the early 1990s, research teams led by Margaret Liu, then of Merck Research Labs (see interview, page 5), made the startling discovery that these bacterial plasmid vectors, when injected into

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IAVI Releases Scientific Blueprint; Bill Gates, U.K. Gov't Provide Support

The International AIDS Vaccine Initiative (IAVI) unveiled a global scientific blueprint to put HIV vaccine development on the fast track. New grants from the William H. Gates Foundation and the British Government, along with funds from previous key donors, will allow IAVI to immediately begin implementing the plan.

In addition to providing a comprehensive, global overview of current AIDS vaccine research and development efforts, IAVI's *Scientific Blueprint for AIDS Vaccine Development* lays out a unique strategy of accelerated product development and human testing through international collaborations. The blueprint also outlines clear timelines and milestones to maximize the likelihood of

success within the next decade.

The report stresses that IAVI's approach is designed to complement, not compete with, existing AIDS vaccine programs, which have increasingly emphasized basic research. The enhanced effort would cost approximately US\$350- \$500 million above current expenditures over the next nine years.

"This is not a trivial amount, but it is tiny compared to the more than US\$18 billion the world spends on AIDS treatment, prevention and research each year," said IAVI's President Seth Berkley. "A vaccine is our only realistic hope for ending this epidemic, especially in developing countries where the costs of treatment are prohibitive."

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Industry Insider

Wyeth Takes Over Apollon

In a move that is likely to have a significant impact on HIV vaccine development, Wyeth-Lederle Vaccines has acquired Apollon, a biotech company specializing in DNA-based vaccine technology. To date, Apollon has been the only company to launch human trials of an HIV DNA vaccine. The company's research program includes candidate vaccines for HIV, herpes simplex, hepatitis B, human papilloma virus, cancer and auto-immune diseases.

George Siber, Vice President of Research & Development for Wyeth-Lederle, will now oversee the Apollon research program. Siber told the *IAVI Report* that "the acquisition will give us a basic DNA technology platform which a large effort in vaccines now requires."

Wyeth, a subsidiary of the pharmaceutical giant, American Home Products, is currently assessing its strategy for HIV vaccine development. "In order to move forward in development of candidate HIV vaccines," says Siber, "we will be looking to access some resources from third parties, either within or outside government." Siber noted that Wyeth is also

working with Barton Haynes of Duke University in developing an HIV peptide vaccine that is now in Phase I trials, and with the National Cancer Institute in studying an adenovirus vector for use as an HIV vaccine.

Apollon had unsuccessfully attempted to launch a public stock offering in 1997. Wyeth, which had made an early investment in Apollon, then decided to acquire the company. It will use Apollon's Malverne, Pennsylvania facility to continue its DNA vaccine research and development.

Glaxo Re-Enters Vaccine Field

Glaxo Wellcome appears to be taking small steps to re-enter the vaccine business. The company announced that it will collaborate with Powderject Pharmaceuticals, another U.K.-based company, in developing gene gun technology that delivers vaccines and therapies to patients by "shooting" them through the skin, without intramuscular injections. Glaxo is making a US\$20 million investment in Powderject and paying the company US\$4 million to license a hepatitis B DNA vaccine that is now in Phase I studies in the U.S. The agreement was

announced in March and caused a 33% rise in Powderject's stock. The gene gun technology is being developed by researchers at Oxford University who include Andrew McMichael (see *IAVI Report*, vol.3, no.1).

Glaxo also maintains a small in-house vaccine development group focused on herpes vaccine development and has licensed a genital herpes vaccine from the U.K.-based Cantab Pharmaceuticals. The herpes vaccine is currently in Phase I trials. Glaxo has also invested in the Jenner Institute, a vaccine research institute in the U.K. Before they merged, both Glaxo and Wellcome sold their vaccine divisions.

More Good News for Vaccine Business

The global media is continuing to report on the upsurge in the international vaccine market. *The Wall Street Journal* (2 February 1998) reported that "the vaccine business is heating up with potentially huge implications for drug industry profits and public health. New bioengineered vaccines—unlike their predecessors are patentable and luring drug companies with the promise of high prices." The overall vaccine market, according to the article, is expected to triple

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HIV DNA VACCINES *continued from page 1*

mice, could protect against challenge with a live virus (influenza). Further research showed that this gene-directed expression of proteins generated protective immune responses in several other animal/disease models.

If DNA vaccine technology shows promising results in human trials, the impact for international HIV vaccine development will be significant. HIV DNA vaccines would likely be more stable and easier to transport than live vector vaccines, and simpler and less costly to manufacture than other vaccine designs. Furthermore, it is theoretically possible to produce a combination of DNA vaccines that protect against several diseases at once, by combining antigen-coding genes from several pathogens into one or more plasmid vectors administered together.

Creating a DNA Vaccine

The first step in creating an HIV DNA vaccine is to identify the HIV genes to be inserted. Options could include: *env* (coding for all or portions of the envelope gp160 proteins), *gag* (coding for

structural proteins such as p24 and p17) and *rev* (a regulatory gene). The *env* gene codes for envelope proteins, which may be important because the outer envelope of HIV is most likely to be recognized by neutralizing antibodies. The *gag* gene may have special importance, though, since *gag* results in expression of internal HIV proteins that are less variable, and these highly conserved proteins may generate CTLs against a wide range of HIV isolates.

To create a plasmid DNA vaccine, researchers isolate the desired HIV genetic sequences corresponding to the HIV gene and recombine or incorporate these sequences into a plasmid, as follows. The HIV genes can be obtained from viral isolates in national research repositories or from patients with HIV. The genetic material is then extracted and purified from these viral isolates. Using specific enzymes, the genetic sequences are transcribed into DNA. Specific sequences are then cut out and inserted into the plasmid DNA. Additional gene sequences can be added to enable the genes to be expressed in human cells and facilitate selection of the bacteria that contains these altered plasmids. The bacteria with the

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plasmid is then grown in large quantities and the plasmid DNA is purified and prepared for use as a candidate vaccine.

When DNA vaccines are injected intramuscularly, antigen presenting cells (APCs) pick up and express the plasmid DNA or acquire the antigen itself in some form. The resulting antigens are “presented” to the rest of the immune system by these cells and, hopefully, stimulate antibody and cellular immune responses against the encoded HIV antigens.

Increasing the potency of DNA vaccines

In order to make DNA vaccines more potent, it may be necessary to increase expression of the incorporated genes or otherwise alter the immune response to more effectively process the expressed protein. Researchers are also exploring a number of specific approaches to increase the potency of these products. These include:

- **Combining DNA vaccines with other vaccine approaches:** To increase immunogenicity, DNA vaccines are being tested in combination with other vaccine approaches. A number of research teams have shown that a “prime-boost” combination – priming with DNA and boosting with an envelope protein – can stimulate both antibody and cellular immune responses in various animal models. Combining DNA with a live viral vector boost is also being studied by a number of research teams. The attraction of this approach is that the DNA can prime for cellular immune responses against the encoding antigen, with the live vector hopefully being able to expand these virus-specific responses. Among those studying a DNA/live viral vector combination are researchers at: Oxford University in the U.K. (DNA plus modified vaccinia Ankara –MVA), the Macfarlane Burnet Centre in Australia (DNA plus fowlpox) and Emory University in the U.S. (DNA plus fowlpox).
- **Using gene guns to deliver DNA vaccines:** DNA vaccines can be administered in a saline solution by direct intramuscular injection. Researchers at Powderject Pharmaceuticals are studying

the use of gene gun technology that delivers DNA on microscopic gold beads and “shoots” these beads through the outer layer of the skin, without the use of a needle. A research team at the Karolinska Institute in Sweden is using a “dental gun”, which is typically used to administer dental anesthesia to children, to deliver HIV DNA vaccines via mucosal surfaces in the mouth.

- **Combining DNA vaccines with cytokines:** Some researchers are studying whether encoding various cytokine genes in DNA vaccines can increase their immunogenicity and drive specific types of immune responses. Data produced by David Weiner’s lab at the University of Pennsylvania suggests that cytokines such as interleukin-2, interleukin-12 and interferon gamma, when expressed in SIV DNA, can increase different types of immune responses in macaques. Specifically, they have found that IL-12 increases CTL responses, IL-2 drives proliferative responses and interferon gamma increases antibody responses.
- **Using bacterial vectors to deliver DNA vaccines:** A number of research teams are studying the use of live attenuated bacterial vectors such as Salmonella and Shigella to deliver DNA vaccines. These bacterial vectors are easy to produce, can be given orally and help generate strong mucosal immune responses. Researchers at the University of Maryland appear to be the farthest along in studying this approach. They have initiated a Phase I study of an attenuated Salmonella vector encoding gp120 and are developing a Shigella vector that encodes an HIV DNA vaccine.
- **Using a “layered vector system”:** One mechanism that may increase the immunogenicity of DNA vaccines is the use of an RNA replicon (a replication-defective virus that is not infectious). Researchers at Chiron Viagene have shown that a DNA construct encoding an RNA replicon from Sindbis virus can

induce immune responses against the antigen that may be more potent than DNA alone.

Human Trials of HIV DNA Vaccines

The few clinical trials of early first-generation DNA vaccines have yet to demonstrate durable CTL or antibody responses in human volunteers.

To date, only two HIV DNA candidate vaccines have been studied in uninfected human volunteers. Both products are

produced by Apollon (recently taken over by Wyeth Lederle Vaccines.) One of these DNA vaccines includes the HIV genes *env* and *rev*; the other incorporates *gag* and *pol*. All the trials have been conducted in the United States, using vaccines based on clade B HIV. A number of knowledgeable sources report that while the Phase I studies of Apollon’s two

The real question is whether industry will pursue development of HIV DNA vaccines if early studies fail to show dramatic results.

HIV DNA vaccines indicate that the constructs are safe, they have, so far, shown minimal CTL responses in uninfected volunteers.

However, the trial of the *gag/pol* construct is still ongoing and the data has not been fully collected. Moreover, CTL responses could increase over time. And it is possible, though unlikely, that the weak immune responses are due to limitations in the assays used to measure CTL levels. It is also possible that more frequent immunization with these vaccines could increase their immunogenicity. Nevertheless, a number of leading researchers contacted by the *IAVI Report* expressed doubt that Apollon’s first generation HIV DNA vaccines, as currently designed, will induce significant CTL response in human volunteers.

Some suggest that “bupivacaine”, an analgesic administered with Apollon’s vaccines to enhance immunogenicity, may be adding little to the immune responses in these trials. However, the company’s patent for DNA vaccines is reportedly based on the use of DNA with bupivacaine. It will be

The Outlook for Key HIV DNA Vaccine Development Programs

by David Gold

A number of companies and research centers around the world are developing HIV DNA vaccines. Some of the key players are described below.

Chiron (US)

Chiron's HIV vaccine program includes a range of DNA products. The company reports that it is exploring alpha virus technology, bacterial vector delivery system, as well as other ways of formulating and delivering DNA. Chiron's existing HIV vaccine program includes gp120 and p24 vaccines that are currently in human trials, as well as a number of different adjuvants.

Outlook: Chiron appears to be focused on developing a technological base to deliver a broad range of DNA vaccines. While the company has yet to launch human studies of any of these products, it claims that it will be far more aggressive in moving early concepts into Phase I human studies. With Margaret Liu (see interview page 5) now overseeing Chiron's vaccine program, the company adds to an already strong group of researchers working on HIV vaccines. Chiron's broad range of candidate HIV vaccines and adjuvants will make it possible to combine approaches. In addition, researchers from Viagene are now being more fully integrated into Chiron and may provide an additional technological boost to the company's vaccine efforts. If Chiron is serious about investing significant resources in HIV vaccine development, it could have a major impact on the effort. One key indicator: how quickly the company can move new candidate HIV vaccines into human trials.

Merck (US)

Merck researchers hope to put an HIV DNA construct into Phase I human studies by November 1998. The company is also conducting preclinical studies of DNA constructs with envelope proteins in macaques. Earlier studies had shown that the DNA/envelope protein prime-boost combination could protect monkeys against a non-pathogenic SHIV virus, whereas DNA or protein alone failed to protect. The current study will challenge the monkeys with the pathogenic SHIV 89.6.

Outlook: Merck has the ability to bring substantial resources to bear in its effort to develop an HIV vaccine. The company's development program contains top-quality scientists and is led by a well-respected researcher who has already brought to market the leading HIV protease inhibitor. Moreover, the company's vaccine division is headed by a recognized leader in the field and a strong advocate for vaccine research. Merck has the resources, and perhaps the will, to move its program forward without U.S.-government support. If the DNA/envelope protein combination protects monkeys from challenge with a pathogenic SHIV strain and the Phase I study shows good CTL response in humans, the company could fast-track development and initiate a Phase III efficacy trial by the year 2000. If the Phase I results are disappointing, it will be interesting to see how Merck proceeds.

Pasteur Merieux Connaught (France)

Pasteur Merieux Connaught (PMC) has licensed DNA vaccine technologies developed by Harriet Robinson while she was at the University of Massachusetts. Robinson's lab at Emory University is evaluating five different DNA constructs in macaques. The vaccines have protected against a non-pathogenic SHIV challenge, with the most potent immunogens being the DNA/envelope protein and DNA/fowlpox combinations. Robinson will challenge the monkeys with a pathogenic SHIV strain very shortly.

Outlook: While PMC is developing a broad range of HIV vaccine approaches, the DNA program does not appear to be on a fast-track development plan. Company officials suggest that human trials could begin within 18 months, but others are more skeptical. However, Robinson is considered one of the top researchers in the field and is reportedly interested in doing a Phase I prime-boost study of HIV DNA with one of PMC's canarypox vectors. And PMC, unlike other companies, has the ability to combine DNA with canarypox vectors that have already been approved for human study. With baseline data on CTL responses generated by

the canarypox vectors already available, PMC could learn very quickly whether a DNA vaccine would have a significant additive effect.

Wyeth/Apollon (US)

Wyeth Lederle has assumed control of Apollon's HIV DNA program which includes a clade B envelope HIV DNA vaccine (encoding *env* and *rev*) and another encoding clade B core proteins (*gag* and *pol*). Apollon continues to collaborate with David Weiner's lab at the University of Pennsylvania, which is studying DNA constructs that encode various cytokines. Apollon is also collaborating with the U.S. Army on efforts to develop HIV DNA vaccines based on non-clade B viruses, possibly for testing in Thailand. The U.S. Army is also testing Apollon's *env/rev* DNA construct in a Phase I human study and doing preclinical work with Weiner on combining DNA and cytokines.

Outlook: Wyeth is currently assessing its entire HIV vaccine program, including the Apollon DNA program. George Siber, who will oversee Wyeth's program, is well-respected in the vaccine field and appears to be taking a strong interest in HIV vaccines. Weiner, for his part, continues to generate interesting and important preclinical data on new DNA approaches for Wyeth/Apollon. Wyeth has the ability to bolster the existing HIV DNA program with significant resources and expertise. The big question is whether it will do so.

Oxford University (UK)

Andrew McMichael's research lab at Oxford is developing a combination approach using DNA priming and an MVA boost. (See *IAVI Report*, vol.3, no.1.) Both constructs encode the same HIV epitopes. The Oxford team has tested the DNA/MVA combination in mice and, early this year, began studies of the prime-boost combination in macaques. Unlike others, this group's focus is on clade A HIV.

Outlook: McMichael recently told the *IAVI Report* that he is seeing "encouraging results" in the macaques immunized with the DNA/MVA combination, in terms of generating CTL responses. With these early results, McMichael's team is now in the

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An Interview with Margaret Liu

Margaret Liu, M.D. is considered to be one of the pioneers in DNA vaccine research. As a senior scientist at Merck Research Labs, her research team published ground-breaking studies on DNA immunization in animal models. In September 1997, Liu became vice-president of vaccine research at Chiron Corporation. In this new position, she oversees the company's vaccine research program and thus can be expected to have a significant influence on overall HIV vaccine research.

IAVI Report: In 1993, your research team published findings that influenza DNA vaccines could protect mice. Are you still optimistic about the ultimate usefulness of this approach?

LIU: It's been incredibly encouraging to see the large number of research papers that have been published on DNA vaccines from different labs, using different model systems, diseases and basic starting plasmids. Many of these papers have shown either immunogenicity or actual protection. Clearly, this is a very robust technology.

But, there are challenges in translating things from the laboratory into the clinic. And, so, my feeling, particularly related to HIV, is that we want to make these DNA vaccines even more potent. That doesn't mean that the first-generation constructs won't work; it just means that — as with anything — you want to keep improving them.

IAVI Report: How would you make a more potent DNA vaccine?

LIU: You can just think about it mechanistically. Start with basic vector design. Maybe you can make better expression levels. And deliver DNA to special cell types, such as immune-presenting cells or antigen-presenting cells. Or package the DNA to protect it from being degraded. These might increase the potency or duration of immune responses.

IAVI Report: In some ways the plasmid DNA is similar to recombinant vector vaccines.

LIU: Yes, but there are also some significant differences. In most vector systems, there's a concern about making anti-vector immune responses. So, for example, it is unclear whether you can use an adenovirus vector made of the same strain of adenovirus seen in common human infections. Or, whether you can use a vaccinia vector in people immunized with a smallpox vaccine.

A second potential issue is the size of the insert you can put in the vector. We

don't know whether or not that's an issue for DNA, but with some viral vectors there are real limitations for what you can do. And manufacturing viral vectors may be much more complicated than making a DNA plasmid.

Now some approaches blur the distinction between vector and DNA systems. A number of researchers are studying bacterial vectors such as salmonella that

deliver DNA vaccines. It's an interesting approach because now you're delivering the DNA mucosally. For HIV, there are real advantages in getting mucosal immune responses. These bacteria vectors differ from other vectors like vaccinia, because you're not actually transcribing the gene as part of the vector; you're using the bacteria to carry plasmids of DNA.

Another area at the interface of vectors and DNA vaccines involves alpha virus replicons. In these replicons, the genes of the antigen of interest is substituted for the structural genes. Alpha viruses make lots of message. So, with the inserted viral particle, you make lots of protein. But the virus doesn't replicate and is not infectious.

There's another technology that even further blurs this line. A group from Viagene (now part of Chiron) made a DNA construct of these alpha viruses. It's just a regular plasmid DNA. But the difference is, instead of just producing your messenger RNA and then your one protein, it now encodes enough of the alpha virus that it makes all the machinery to amplify the messenger RNA.

So, there are now three different approaches that are at the interface of vector and DNA — bacterial vectors, the

alpha viruses and the layered expression vector systems based on the alpha viruses.

IAVI Report: What are alpha viruses?

LIU: Examples are Venezuelan equine encephelitis virus (VEE), Semliki forest virus and Sindbis virus.

IAVI Report: Some people have suggested that the early human studies of HIV DNA vaccines have shown disappointing immunogenicity.

LIU: I can't really comment on that, because I am not involved in these studies. My understanding is that some of the studies will be described at upcoming meetings.

At Merck, part of the reason we didn't test an HIV DNA early on was that we wanted to optimize the protein expression of the vector. So, I wouldn't be too discouraged by early studies on HIV, because many of the early DNA plasmids had very low levels of expression relative to what you could obtain.

IAVI Report: Can DNA vaccines generate significant antibodies?

LIU: One of the reasons that I am so committed to a gene approach — it doesn't have to be DNA, it could be an RNA approach for encoding the gene — is that I think CTL responses are very important. And the DNA approach seems to be quite good at generating them.

But antibodies are also likely to be important. DNA vaccines prime very well and generate antibodies. The studies we did in influenza, as well as studies by various laboratories in other systems such as HIV, show that DNA vaccines can generate T-cell and B-cell epitopes that are different than those seen when using recombinant proteins. And with influenza, in some cases, we got a broader response with DNA than with a killed virus.

My envisioned vaccine for HIV is some type of gene delivery, followed by a recombinant protein boost plus an adjuvant.

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A number of research teams have shown that priming with DNA and boosting with a protein seems to be a very good combination for getting very high antibody titers. So, while DNA certainly elicits good antibody titer, with HIV, the prime boost combination appears better than either modality alone.

IAVI Report: Could you tell us a little bit about Chiron's HIV vaccine program?

LIU: We have a significant effort being devoted to HIV and it involves both clinical and basic research.

For envelope, in the clinical area we are continuing human studies of gp120, and in the basic area, we are working to make antigens that will give us broader neutralizing antibody responses. We are comparing different constructs with gp120. It's always possible that you don't need oligomers.

And, obviously, we have a very broad-based program focused on ways of delivering genes to get cellular responses. It's actually not just naked DNA. I've sort of moved past that. So, in terms of anybody getting upset about patents and licenses, it doesn't matter because that's not really our focus.

We're looking at a range of technologies, including the alpha virus technology, the bacterial vector delivery system, as well as other ways of formulating DNA to deliver it. The real focus is a technology base, that will be broadly applicable to HIV and other diseases.

We also have a big adjuvant program. My envisioned vaccine for HIV is some sort of gene delivery, followed by boosting with some form of recombinant protein with an adjuvant. And we're considering mucosal versus systemic delivery of the vaccine.

IAVI Report: You have a bivalent clade E and B gp120 trial starting in Thailand.

LIU: That trial started this year. You know, we recently observed in primates, that while a clade E gp120 generated antibodies that neutralized several clade B isolates, the clade B gp120 couldn't generate such cross-clade neutralizing antibodies.

Now, the clade E strain is a primary isolate, and the clade B strains it neutralized were lab isolates. We haven't yet gotten

antibodies that neutralize primary isolates. But it was still a very exciting observation. It also points up that so much work has focused on clade B and laboratory isolates of HIV and what we see with them may not be reflective of other isolates.

Of course, the clade E gp120, as a primary isolate, may be presenting some novel conformational epitopes that allow it to have the cross-clade neutralizing ability, while the clade B gp120 is based on a lab isolate.

IAVI Report: There were reports that the gp120 program is not terribly secure within the company.

LIU: Apparently, rumors have been spread that we've pulled out. This is completely untrue.

As I mentioned, we have an active, broad-based HIV envelope program, both in the basic area and in the clinic. We just wanted to take a step back and do studies comparing different forms of envelope, to see whether we can get more breadth if we use oligomers, primary isolates or other mechanisms.

But we are continuing with all our commitments in the prime-boost studies, and, in fact, are providing gp120 for the upcoming Phase I study of Pasteur Merieux's new canarypox constructs for Thailand. The only thing that we have said is that we would like to see the Phase II results before we decide whether to go on into Phase III.

IAVI Report: Which is what PMC has said, too.

LIU: Precisely. That is why you do Phase II studies before Phase III. We're not going to manufacture all these doses and spend millions of dollars, when we don't yet know whether the clinical data will warrant it. Or whether NIH or Pasteur Merieux, with whom we have good relationships, want to go ahead with the study.

IAVI Report: Do you think, on its own, the existing gp120 vaccines can protect?

LIU: I wouldn't rule it out, but that's not what we're envisioning as a vaccine. I think

a cellular response is going to be a key component. You obviously get cellular response against gp120 by using DNA modalities, but you might as well use some of the more conserved proteins.

IAVI Report: Chiron also has a p24 vaccine.

LIU: Yes. We are completing a Phase I clinical trial of p24. But, again, the analogy would be gp120 compared to a more full-length envelope. We'd like to use more of the rest of the protein, if possible.

IAVI Report: How far are you from a human study of a gene based construct?

LIU: I try not to speculate.

IAVI Report: But we like speculation.

LIU: I will tell you that the key issue for all these technologies, once we show they're safe, is to be as aggressive as possible about moving into human studies. You can do all the animal studies you want, but what really counts is what happens in people. So, for a disease like HIV, where the need for a vaccine is so desperate, we are changing our approach to be more aggressive about moving into the clinic. By doing so, we believe we can accelerate the pace of things.

IAVI Report: What about the idea of using cytokines with a gene-based vaccine?

LIU: That may be a useful approach. But from a regulatory standpoint, at least for now, it might raise some concern for a first generation DNA vaccine unless you could demonstrate very good regulation of the expression. So, from our perspective, it's not something we envision for a prophylactic vaccine at this stage.

IAVI Report: Do you think there will be significant safety concerns with gene-based constructs?

LIU: The biggest hurdle has been overcome, in terms of putting a recombinant DNA vaccine into healthy individuals. Assuming that the Phase I studies continue to demonstrate safety, it's just a question of demonstrating safety for each individual technology through well-designed preclinical studies.

IAVI Report: What is the view of Chiron's

We are changing our approach to be more aggressive about moving into human studies.

AIDS in South Africa: An Interview with Salim Abdool Karim

Salim Abdool Karim, M.D. is the director of the Centre for Epidemiological Research in South Africa. Karim has closely followed the emerging AIDS epidemic in South Africa since the mid-1980s. His research team was also recently selected as an international HIVNET site by the U.S. NIAID. If HIV vaccine trials are conducted in South Africa, Karim will likely be one of the key investigators involved in the studies.

IAVI Report: Where is the AIDS epidemic in South Africa at this point?

KARIM: The epidemic first established itself in the general population in South Africa much later than it did in central Africa, most likely in the late 1980s and early 1990s. Our research team looked at several hundred blood specimens taken from 1986 to 1988 and couldn't find any that were HIV-positive. But in the samples taken in 1991, we started seeing some evidence of HIV infection.

Since then, HIV has spread at an explosive rate in South Africa. Looking at data from annual surveys of pregnant women attending antenatal clinics, we see that in 1997, HIV prevalence among these women was over sixteen percent.

When you consider that it went from below one percent to sixteen percent, in something like seven years, it gives you an idea of the explosive spread of the epidemic in our country. And it is particularly severe in some provinces, such as Kwa Zulu Natal. Our testing of more than a thousand women each year in that province shows a current HIV prevalence rate among pregnant women of about thirty-five percent.

IAVI Report: What do you think has made the epidemic so explosive in South Africa compared to other countries?

KARIM: I don't have an exact answer, but I can suggest some factors. I ascribe it mainly to the sociological phenomenon of the internal migration in South Africa. The apartheid system created what is called "oscillating migration", where workers take jobs in the cities or in the mines and live in single-sex hostels.

They leave their wives and children in the rural areas, and don't see them for quite long periods of time. You have a situation where hundreds of thousands of young men, in the prime of their lives, are put in a setting where they do not have their regular partners, thereby creating conditions for prostitution. Then these men go home, at regular intervals, and create opportunities for spreading the virus in that way, as well.

Secondly, the highest incidence of HIV is in young people, from the age of sixteen to twenty-five. This group has no sense of future in South Africa. It's going to take quite a while for us to build a sense of hope in the future for this generation.

In South Africa, they're sometimes called the lost generation. They are, unfortunately, products of a very poor and disadvantaged education system. They come out of that situation,

with an unemployment rate of around thirty percent and no prospects for jobs or advanced education. There is no sense of looking forward to the future. So it's very hard to promote health messages that say "put off today's pleasures for a better tomorrow." It just doesn't work in that setting.

And the third reason is the very high prevalence of STDs in South Africa. Studies we've done in rural communities show that, at any one time, about one-quarter of women in the reproductive age group have an STD. That is a huge percentage and it contributes to the ease at which HIV is transmitted.

IAVI Report: How does the AIDS epidemic in South Africa compare to that in neighboring countries?

KARIM: Some of our immediate neighbors have also experienced a rapid growth in the epidemic. In Botswana, for example, HIV has spread very rapidly as measured by antenatal clinic prevalence rates.

But in some countries, such as Mozambique, the epidemic has been slow to take off. Because of the war, Mozambique is very compartmentalized, so the epidemic hasn't taken hold as quickly as it has in South Africa.

And among some of our other neighbors, the epidemic has reached a steady state while continuing to spread. These countries are already seeing high death rates from AIDS.

IAVI Report: You've probably seen a particularly rapid spread among commercial sex workers.

KARIM: Yes, we've published several studies about the incredibly high incidence rates of HIV infection in this group. We are currently studying a vaginal microbicide in a cohort of sex workers working at truck stops. In this cohort, where there's been a lot of health promotion and encouragement of condom use, roughly ten percent are still becoming infected each year.

IAVI Report: Aren't there really two separate epidemics in South Africa?

KARIM: That's right. We saw the first cases of AIDS in the mid-eighties, when we started seeing Kaposi's sarcoma and pneumocystis carinii pneumonia, diseases that we were just not familiar with. These were occurring mainly among white, gay men. It was only much later, in the early 1990s, that we started seeing the epidemic take hold in the heterosexual community.

Mass internal migration, generated by the apartheid system, has contributed to the explosive spread of HIV in our country.

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South Africa's Explosive AIDS Epidemic

South Africa is considered by many to have the world's fastest-growing AIDS epidemic. It is now estimated that at least 50,000 South Africans are becoming infected with HIV each month.

The epidemic, according to South Africa's Minister of Health, Nkosazana Zuma, has most severely impacted the country's young and most economically active people. "While no age level has been spared," Zuma recently told South Africa's Parliament, "the worst hit are in the 15- to 40-year bracket." A national survey in 1997 revealed that approximately 16 percent of pregnant women attending ante-natal clinics were carrying the AIDS virus, compared to 14 percent in 1996.

"AIDS is the single biggest threat to South Africa's social stability, economic prosperity and to our very survival as a nation," Zuma said. "The problem is so serious and the consequences so dire that we have no choice but to work together for the good of our nation and our common future," she added.

According to many researchers, sociological factors such as marginalization, discrimination and alienation, all contribute to increased vulnerability to HIV infection. This is nowhere more starkly demonstrated than in South Africa - where blacks, and particularly, black women are hardest hit by this epidemic. Data from voluntary blood donors in the country demonstrate that while HIV is spreading in all race groups, it is about 10 times more common among blacks compared to other race groups.

Background

The first cases of AIDS in South Africa occurred among homosexual men and blood transfusion recipients in the early 1980's. But even by 1985, HIV testing of stored samples from blood donors showed a very low prevalence of HIV in the general population.

HIV-1 is the dominant strain in South Africa, with HIV-2 remaining rare. Clade B virus predominates among gay men, and clade C is associated with transmission through heterosexual contact. Thus, two independent HIV epidemics appear to be unfolding in South Africa; the first epidemic started in the early 1980's and has spread mainly through male-to-male sexual contact and infected blood supplies, while the second, and far larger epidemic, started in about 1987 among heterosexuals and in children infected through perinatal (mother-

to-infant) transmission. Injecting drug use does not appear to be a very important mode of HIV transmission in South Africa.

Trends in the Epidemic

Although current HIV data are patchy and incomplete, the annual, national survey of pregnant women attending antenatal clinics provide a picture of the rapidly emerging epidemic in South Africa. Among antenatal clinic attendees, HIV prevalence has risen more than 15-fold from 0.76% 1990 to 16.1% in 1997.

In total, it was estimated that, at the end of 1995, almost 1.8 million South Africans were infected with HIV.

Geographical distribution

The HIV seroprevalence surveys demonstrate large differences in the rates of HIV infection across South Africa, from high levels in the north eastern provinces, to lower levels in the south western parts of the country.

Mother to child transmission

Breastfeeding appears to be a major factor in transmitting HIV in South Africa. Recent studies estimate that in Durban, where breast feeding is the predominant infant feeding practice, 34.7 % of infants born to HIV-positive mothers become infected. A study of 163 mother-infant pairs in Soweto found that 18% of the formula-fed infants were infected with HIV, as opposed to 46% of the breast-fed infants.

STD clinic attendees

HIV prevalence among STD (sexually transmitted disease) clinic attendees has increased rapidly in South Africa. In Carletonville, a mining community, HIV prevalence among STD clinic attendees increased from 8% in 1991 to 44% in 1996. And ongoing

monitoring of STD clinic attendees in rural Hlabisa found that in 1996 about 40% were co-infected with HIV.

A 1996 study at an STD clinic in Johannesburg found that 25% of men with a urethral discharge were infected with HIV compared to 44% of women. At the same clinic, 48% of all patients with genital ulcers were infected with HIV.

Sex workers

Commercial sex workers are obviously at very high risk for HIV in South Africa. A study conducted in 1992 at an escort agency in Durban found no HIV infection among sex workers. However, in a survey of 145 female sex workers at truck-stops in the Natal Midlands conducted in 1996, 50.3% were reported to be HIV-infected. When researchers explored some of the issues relating to sex work at truck-stops, it was found that insistence on condom use by sex workers resulted in loss of clients, loss of income or experience of violence.

Research suggests that the clients of sex workers also need to be the focus of interventions. A study of 213 long distance truck-drivers passing through the Natal Midlands indicated that 27% had an STD at some time; 18% reported swollen glands; 25% have sex during an STD infection; 71% never use condoms and 35% have more than 1 partner.

TB clinic attenders

The most common HIV/AIDS presenting opportunistic infection in South Africa is tuberculosis (TB). In Hlabisa, co-infection with HIV in adult TB patients rose from 8.7% in 1991 to 70% in 1997. At one hospital in Gauteng, in 1997, 60% to 80% of newly admitted TB patients were co-infected with HIV.

Future Projections

Unless something is done to change the course of the epidemic in South Africa, the country is likely to be devastated by HIV over the next ten years. One study projects that if current trends continue the country will have more than 2.8 million HIV-infected adults by the year 2000 and 4.5 million by the year 2005.

Not surprisingly, a steep rise in mortality rates is also projected, as increasing numbers of HIV-infected individuals progress to AIDS. And as growing numbers of parents die, there will be a huge rise in the number of orphans. By the year

HIV Infection in Women Attending Antenatal Clinics in South Africa

YEAR	HIV PREVALENCE (%)	YEAR	HIV PREVALENCE (%)
1990	0.76%	1994	7.57%
1991	1.49%	1995	10.44%
1992	2.69%	1996	14.07%
1993	4.69%	1997	16.01%

Source: Epidemiological Comments, 1997

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And if you look at genotyping, the virus in the gay community is predominantly clade B; and in the heterosexual community, it's predominantly clade C. So, we have two parallel epidemics.

IAVI Report: Are there differences in HIV-incidence based on race?

KARIM: Yes, though we don't have really good data. The antenatal surveillance gets too few white and Indian women to make a substantial comment. But blood bank data suggests that the epidemic is growing at a much more rapid rate among blacks. However, it is present and growing in all race groups.

IAVI Report: Can you tell us about your work.

KARIM: I run the Centre for Epidemiological Research, which is part of the Medical Research Council of South Africa. During the early stages of the epidemic, much of our work focused on describing the epidemic. We found that women are more likely to be infected and at earlier ages. So we needed to target this group, if we were to make any impact on this epidemic.

We've also set up a cohort of sex workers for the microbicide study. And with NIH funding, we've set up a trial of improving the treatment of sexually transmitted diseases (STDs) in a rural community. It's a randomized controlled trial. The idea is to look at the impact of STD treatment on the spread of HIV.

In 1996, we received a large grant for reproductive health, from the Wellcome Trust. We have several studies looking at HIV that are funded by the trust. And last year, we received a HIVNET grant from NIH. This has helped us do mother to infant transmission studies, with a focus on breast feeding. The AZT maternal fetal transmissions studies are based on the assumption that the woman won't breast feed. Yet in our setting, more than two-thirds of women breast feed. They have to because they don't have the opportunity to prepare formula-feeding.

IAVI Report: So, even if a woman knows

she's HIV-positive, she is probably breast feeding her infant?

KARIM: Right. Purely because she has no other option. If people think we have solved the vertical transmission problem, they are wrong — we haven't.

IAVI Report: Are there any plans for trials of candidate HIV vaccines in South Africa?

KARIM: Our HIVNET application was based on our desire to do vaccine trials. We're now getting a clearer understanding of how to do this, based on our discussions with NIAID, IAVI and UNAIDS.

Almost all research is still focused on clade B HIV vaccine candidates. While, some studies suggest that clades might not be so important, we don't know for sure. What we do know is that most of the new HIV infections in the world are going to be with clade C strains. Both South Africa and India face rapidly spreading epidemics with clade C HIV.

Our research team will be working towards demonstrating the capability to do Phase I, II and III trials. That is not going to be easy, but with the three partners that we now have, we're hopeful.

IAVI Report: Are there any biomedical research establishments in South Africa that are looking at doing vaccine development?

KARIM: We have a group in Cape Town that has been actively involved in genotyping the virus. But there is no private vaccine manufacturer or academic institution that is actively pursuing vaccine development.

IAVI Report: And how has the government responded to the epidemic?

KARIM: It's been a mixed bag. The government has been going through a fairly difficult period. On one hand, we have to transform our country, in terms of bringing in new ideas, new people and undoing the wrongs of the past. But at times, quick fixes, such as the drug virodene, are being pursued. We seem to move from one controversy to the next. And now the Health Minister is thinking

of declaring AIDS a notifiable condition. So, that's going to cause yet more controversy.

IAVI Report: What's your sense of how vaccine trials will be viewed in your country?

KARIM: We're really quite amazed at how much people know. We thought they wouldn't understand these complicated concepts.

There are concerns about becoming infected from a vaccine. And whether a positive HIV test would compromise their ability to get their health insurance or life insurance. But there's an overwhelming keenness to learn about AIDS vaccines, participate and make a contribution.

What has helped is a very strong community lobby that is being developed from a partnership between IAVI and the National AIDS Committee of South Africa (NACOSA), which is a coalition of AIDS organizations.

And this partnership has put HIV vaccines on the agenda. That's good. We need more public debate and information. The better informed our communities are, the easier it will be to undertake trials, when candidate vaccines are available. People are starting to realize that without a vaccine, our country, and countries like ours, will be decimated by this epidemic. ♦

AIDS EPIDEMIC continued from page 8
2000, it is estimated that approximately 200,000 South African children will become orphans due to the AIDS epidemic. This is likely to increase to more than 900,000 by the year 2005. ♦
Editor's Note: Much of the information in this article is excerpted from a report prepared by Quaraisha Abdool Karim of the Fogarty AIDS International Training and Research Programme (and a consultant to IAVI), Salim Abdool Karim, Cathy Mathews and David Wilkinson of the Centre for Epidemiological Research and Sally Gutmacher of the University of Cape Town.

interesting to see whether Wyeth Lederle's purchase of Apollon will provide its researchers with more options in terms of combining DNA constructs with other delivery systems.

But regardless of how its first-generation HIV DNA vaccines ultimately perform, observers agree that Apollon has made a significant contribution by launching the first human trials of HIV DNA vaccines. Companies seeking regulatory approval for Phase I studies of HIV DNA vaccines may now face significantly fewer hurdles in moving their products forward.

Researchers at both Apollon and the Karolinska Institute in Sweden have initiated Phase I trials of HIV DNA vaccines in HIV-infected human volunteers. The Swedish researchers, led by Britta Wahren, recently published data in *The Lancet* (2 May 1998) showing that three different HIV DNA constructs (encoding *rev*, *tat* or *nef*) could generate a measurable increase in CTL responses in HIV-infected volunteers. However, observers note that individuals infected with HIV are likely to have different immune responses to HIV vaccines than uninfected individuals.

Another closely watched DNA vaccine trial is Merck's Phase I study of an influenza DNA construct. The immunogenicity of this first generation vaccine has reportedly been somewhat disappointing. But the results have still not been formally released and there still may be useful data emerging from this study.

In addition to Apollon/Wyeth's efforts, other companies with HIV DNA vaccine programs at earlier stages of development include Merck, Chiron and Pasteur Merieux Connaught. Merck, in particular, is reported

to be planning a Phase I trial in the United States that could begin by November 1998.

In preclinical research, DNA vaccine products are being tested in the macaque/SIV model at a number of key research centers in the U.S., the U.K., France, Sweden and Australia. Virtually all of the HIV DNA vaccines being developed are based on clade B strains of HIV (which are found predominantly in North America and Europe.)

Overall, most researchers appear reluctant to judge the entire DNA approach on a small number of clinical studies of first-generation constructs. Harriet Robinson, a researcher at Emory University who is developing DNA constructs for a number of diseases, predicts that DNA vaccines are likely to be included in any AIDS vaccine that is ultimately developed "simply because they so powerfully induce critical CTL responses."

But one leading NIH scientist cautions that "it is the nature of vaccine development to see failure, even spectacular failure, early in the process. With a new approach, such as this, it would be astonishing to see clear success in the very first human trials."

The real question, this researcher suggests, "is whether the key industry players have the discipline and commitment to continue to pursue long term development of HIV DNA vaccines even if early studies fail to show dramatic results." ♦

The on-line web site: www.genweb.com provides useful information on DNA technology. The United States FDA has published "Points to Consider on Plasmid DNA Vaccines", available at: www.fda.gov/cber/cberftp.html.

new CEO towards vaccines?

LIU: I haven't yet discussed it with him directly, but certainly the commitment is there from everybody, including our chairman and founder.

IAVI Report: You have a unique perspective, having worked at a major pharmaceutical company and a major biotech company. Why are so few companies investing in HIV vaccines?

LIU: Well, there aren't many companies investing in vaccines, in general. Until the last few years, vaccines were not considered a good investment. The healthcare system in the U.S. still undervalues prevention. People would rather treat the disease than do something to prevent it.

And, frankly, it was only the companies with a longstanding commitment, in terms of their fundamental values, that made the commitment to vaccines. Merck and Chiron are really some of the rare birds in that regard.

In addition, there was some discouragement in terms of developing an HIV vaccine. Now, while it still isn't absolutely clear that you can successfully make a vaccine for HIV, it's becoming much more encouraging.

IAVI Report: One analyst was recently quoted in the *San Francisco Chronicle* as questioning whether Chiron was really serious about vaccines.

LIU: Chiron is clearly committed to vaccine development. You can see that based on how we spend our money. We recently completed the purchase of a European vaccine company. That was not an insignificant investment. And we just sold our vision division to focus more on the core areas of the company, such as vaccines. Remember that Chiron was basically founded as a vaccine company.

IAVI Report: Recent articles in business publications have noted that vaccines are now a growing profit center for companies.

LIU: Yes, and it is much better to be at a company that has had a longstanding commitment to vaccines, before they became trendy ♦.

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VaxGen Gets Approval for U.S. Trial; Still Waiting for Thai Go-Ahead

VaxGen, a California-based biotechnology company, announced in June that it has received U.S. Food and Drug Administration (FDA) approval to launch a Phase III efficacy study of one of its bivalent gp120 vaccines. The trial, which will be the first large-scale efficacy study of an AIDS vaccine, will enroll individuals at "high-risk" for HIV infection in the U.S.

As reported in the *IAVI Report* (vol. 3, no. 2), VaxGen is planning Phase III studies of its bivalent (based on two HIV strains) gp120 vaccines in the U.S. and Thailand. The vaccine to be tested in the U.S. contains gp120 from two strains of clade B virus. (One is the MN strain used in VaxGen's earlier gp120, the other is a strain known as "GNE8".) The construct the company hopes to test in Thailand is based on the clade B/MN strain and a clade E primary isolate strain known as "A244."

IAVI's President, Seth Berkley, praised the launching of the trial, noting that "IAVI is pleased to see this process is beginning. However," he cautioned, "we will need multiple vaccine efficacy trials, in both industrialized and developing nations."

VaxGen is planning to enroll 5,000 sexually active gay men and sero-discordant couples in the U.S. study. The company expects to begin inoculations at five U.S. sites in June. These initial sites will be in Denver, Los Angeles, Philadelphia, Chicago, and St. Louis. The trial will expand to 10 sites within three months and, eventually, to a total of 30.

In looking for investigators for the study, VaxGen is negotiating with many researchers who also work within the U.S.

National Institute of Allergy and Infectious Diseases' HIVNET and AVEG vaccine testing networks. Trial organizers expect to take one year to recruit participants and three years to determine the vaccine's effectiveness. Two-thirds of the 500 participants will receive the vaccine, one-third will receive a placebo. Organizers will provide some safe-sex counseling and education, but are projecting a rate of new HIV infections of approximately two to three percent in volunteers.

In its Thailand trial, VaxGen hopes to enroll 2,500 injection drug users (IDUs). The company has already submitted a "pre-proposal" to Thai authorities. According to Nath Bhamarapavati, a leading researcher and chair of the country's National AIDS Commission's Subcommittee on HIV Vaccine Trials, the pre-proposal is currently being evaluated by "in-country and out-of-country consultants."

But the full proposal has not yet been formally submitted to Thai authorities. VaxGen will need the approval of institutional review boards at each site. The Governor of the Metropolitan Bangkok Authority will also have to give final approval for the trial. Bhamarapavati, who is also a member of IAVI's Scientific Advisory Committee, said that FDA approval of the U.S. trial "is a helpful sign for us, but the trial here still has to go through our approval process and that is not an absolute certainty. An important issue for us," he said, "is whether we would be able to learn how to manage a Phase III trial, particularly in this group."

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The *IAVI Report* is published quarterly by the International AIDS Vaccine Initiative. Funding for publication of the *IAVI Report* is provided, in part, by a grant from UNAIDS. To obtain a subscription to *IAVI Report*, send name and address, by e-mail to: iavireport@iavi.org; by fax to: 1-212-643-0480; by mail: IAVI, 810 Seventh Avenue, 31st floor, New York, NY 10019, USA. Copyright © 1998. All rights reserved.

OUTLOOK *continued from page 4*

process of planning a Phase I study of the DNA/MVA combination in humans. Oxford researchers have created a U.K.-based company, to develop the DNA/ MVA combination.

Karolinska Institute (Sweden)

Britta Wahren of the Karolinska Institute has tested a broad range of HIV DNA constructs in mice, rabbits and rhesus. In May, her team published data showing that three different HIV DNA vaccines (encoding *env*, *rev* and *tat*) could generate measurable CTL responses in HIV-infected human volunteers. Wahren's group has also collaborated with a Japanese research team, led by Kenji Okuda of Yokohama City University, in conducting preclinical studies of a num-

ber of diverse DNA vaccines. The Karolinska team is also using a dental gun to deliver HIV DNA vaccines mucosally. The gun is being used to deliver a second phase of immunizations in the study in HIV-positive individuals.

Outlook: The work of the Karolinska team, which is funded by the Medical Research Council of Sweden and by a grant from the European Commission, could yield important information on HIV DNA immunization. Moreover, their success in initiating a human study of different HIV DNA constructs and publishing the data fairly quickly is a notable achievement. Wahren hopes to begin studies of HIV DNA constructs in uninfected volunteers within six months to a year. ♦

VACCINE BRIEFS

AVAC Issues "9 Years and Counting" Report; Appoints Sam Avrett Director

On 18 May, 1998, the one-year anniversary of U.S. President Bill Clinton's call for development of an AIDS vaccine within the decade, the U.S.-based AIDS Vaccine Advocacy Coalition (AVAC) released a report "9 Years and Counting: Will We Have an AIDS Vaccine by 2007?" To obtain a copy of *9 Years and Counting*, send US\$10.00 to: AVAC, 1875 Connecticut Ave., NW, #700, Washington DC 20009 USA or visit AVAC's website at: www.vaccineadvocates.org.

AVAC also announced the appointment of Sam Avrett as the group's first executive director. Avrett previously served as

Associate Scientific Director of IAVI.

Victor Zonana Joins IAVI

Victor Zonana has joined IAVI as Vice President for Public Affairs. Zonana had previously served as Deputy Assistant for Public Affairs at the U.S. Department of Health and Human Services. He is also an award-winning reporter, first for *The Wall Street Journal* and later for the *Los Angeles Times*, where in 1988 he originated a beat covering the political, social and economic aspects of AIDS.

Penelope Anderson has also joined IAVI as the office manager of the New York office.

SCIENTIFIC BLUEPRINT *continued from page 1*

Berkley stressed that the incremental activities envisioned by the blueprint would be accomplished not just by IAVI, but also by industrial partners, venture capitalists, international agencies and governments of industrialized and developing nations.

"The world is not on track to meet the goal of a safe and effective AIDS vaccine in the next decade," said Margaret Johnston, IAVI's Vice-President for Scientific Affairs. "Accelerated product development and clinical testing, in addition to the increased attention to basic research that we are seeing, offers the best hope of identifying an effective AIDS vaccine in the shortest time possible."

The blueprint calls for the rapid, definitive testing of safe, promising vaccine candidates in humans, an approach described as "thoughtful empiricism." It also proposes creating new entities called International Product Development Teams to foster true partnerships between industrialized and developing countries in vaccine research and development.

Berkley also announced a number of unrestricted major grants to IAVI that will help it to begin immediate implementation of the blueprint. These include a US\$1.5 million grant from the Gates Foundation, the charitable

foundation established by Microsoft founder Bill Gates and his wife Melinda, and a contribution of £200,000 from the Department for International Development (DFID), the international development arm of the British government.

"These represent IAVI's first major grants from a private individual and a government, respectively," Berkley said. "We salute Bill and Melinda Gates and the British Government for their leadership."

Other key supporters of IAVI include the Rockefeller Foundation, the Starr Foundation, the Alfred P. Sloan Foundation, Until There's A Cure, the World Bank, UNAIDS, the Merieux Foundation, the Levi Strauss Foundation and Glaxo Wellcome.

The new gifts, which bring IAVI's unrestricted funds and commitments to approximately US\$15 million, will enable IAVI to create the first of three to six Product Development Teams envisioned by the blueprint.

Key findings and recommendations of the blueprint include the following:

- Multiple efficacy trials of different vaccine approaches around the world must begin within the next five years if we are to develop an effective AIDS vaccine within the decade.
- Very few manufacturers have been willing to commit to testing multiple

vaccine concepts in human trials.

- Despite the desire to have a balanced, multiprong approach of research and development of multiple vaccine designs, support for basic research continues to dominate national AIDS programs.
- Few novel designs are entering Phase I trials and fewer still that have been designed for testing and use in developing countries.
- Involving developing countries in all stages of vaccine development is essential. ♦

IAVI's Scientific Blueprint for AIDS Vaccine Development is available on the web at: www.iavi.org. For copies, fax request to: 1-212-843-0480; or by e-mail: www.info@iavi.org.

INDUSTRY INSIDER *continued from page 2*
to about US\$9 billion per year over the next 10 years. *The Economist* (9 May 1998) noted that the increase in vaccine revenues "has made even the big drug companies sit up and take notice." Key diseases being targeted include: infant diarrhea, human papilloma virus, ear infections, lower respiratory infections, herpes, gonorrhea, gastric ulcers, Lyme disease, dengue fever, and, in some cases, HIV. In financial news, Merck, SmithKline and Rhone Poulenc (the corporate parent of Pasteur Merieux Connaught) all reported record vaccine revenues for 1997. ♦