

# IAVI REPORT

A Newsletter on International AIDS Vaccine Research

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## Proposed Live HIV Vaccine Trials Face Safety, Production Hurdles

*U.S. and Australian groups hope to initiate human studies*

by David Gold

While a physicians' group and a University of Massachusetts researcher each proposed human studies of a live attenuated HIV vaccine, other researchers warned of the risks posed by the studies and a U.S. company said it could be two years before a product was even ready for testing. At the same time, an Australian research team said human studies of its live attenuated HIV vaccine could begin within 18 months.

The flurry of activity surrounding live attenuated HIV vaccines began in September, when the Chicago-based International Association of Physicians in AIDS Care (IAPAC) announced that more than 50 individuals had volunteered to participate in a study of a live attenuated vaccine, first described by Ronald

Desrosiers of the Harvard Medical School (see interview page 6).

Desrosiers and other research teams have shown that live attenuated SIV vaccines could provide impressive protection in monkeys. But concerns began to mount with reports that some newborn and adult monkeys developed simian AIDS from the vaccines (see *IAVI Report*, vol. 2, nos. 1 and 2).

To date, at least four research groups report monkeys that show signs of immune suppression after receiving a live attenuated SIV vaccine. These groups include the Aaron Diamond AIDS Research Center, the Dana-Farber Cancer Institute, the Walter Reed Army Institute of Research and Desrosiers' own lab at the New England Regional Primate Center. The

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## 2,500 Meet in Manila for AIDS in Asia Congress

by James Snodgrass

On 25-29 October, 1997, more than 2,500 delegates gathered in Manila, the Philippines, for the 4th International Congress on AIDS in Asia and the Pacific. Key areas of discussion at the meeting included the explosive spread of HIV in many parts of the region and the need to move candidate HIV vaccines into human studies.

According to IAVI's scientific director, Peggy Johnston, Thailand could well be the location of the first large-scale efficacy trials of candidate HIV vaccines - and sooner than many might think. Speaking at an IAVI-sponsored media

briefing, she suggested that "if everything is safe and works...the first efficacy trial could start in Thailand, perhaps by the year 2000." Johnston also strongly praised the Thai effort, noting that the country "has shown international leadership in developing HIV vaccines."

Prasert Thongcharoen, a virologist at Mahidol University in Bangkok, also speaking at the briefing, noted the urgent need for a vaccine in Asia. The Thai researcher suggested that many in his country were willing to volunteer for a vaccine efficacy trial. "We cannot wait for Western

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monkeys received SIV with deletions in either the *nef*-gene (delta-*nef*) or three genes, including *nef* (delta-3). The initial report that the delta-3 vaccine could cause AIDS in newborn monkeys was made in 1995 by Ruth Ruprecht of Dana-Farber.

These reports led some researchers, including Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) and Barry Bloom, chair of the UNAIDS Vaccine Advisory Committee, to publicly suggest that human studies of the live attenuated vaccines volunteers should not begin at this time.

### NIH meeting

Proponents of the live attenuated trials met with officials at the U.S. National Institutes Of Health (NIH) on 25 September to explore ways of "moving the live attenuated approach forward." IAVI's scientific director, Peggy Johnston, also attended the meeting. According to participants, a number of key questions, beyond safety concerns, were identified. These

questions included: 1) whether any company would be willing to produce a live attenuated HIV vaccine; 2) whether the U.S. Food and Drug Administration (FDA) would approve a manufacturing plan and clinical trial protocol for such a vaccine; 3) how an informed consent process might be developed that would accurately describe the potential risks from the trial; and 4) what party would be responsible for adverse events caused by the vaccine.

### Two U.S. trials proposed

IAPAC presented details of its proposal to bring a live attenuated HIV vaccine into human studies at a conference in Washington, DC on 12 November. As proposed, the trial would use a live vaccine designed by Desrosiers that contains HIV with at least four genes deleted: *nef*, *vpr*, *vpu* and the binding site for the transcription factor, nuclear factor B (delta-4). Initially, five individuals would be vaccinated. If these individuals maintain low levels of HIV after six months, the trial would be expanded.

A different type of study is being proposed by John Sullivan, a researcher at the University of Massachusetts Medical School. He suggests that the first study of delta-4 construct should be in terminal cancer patients. The study would last 6 to 12 months. Only patients with solid tumors for which there is no therapy would be enrolled. According to Sullivan, since many terminal cancer patients have competent immune systems with normal CD4 counts, important information could be obtained from the trial. The University of Massachusetts researcher expects to have little difficulty in attracting volunteers and suggests that "this type of trial could teach us important information about early immune responses and viral replication in the volunteers. It would be an excellent prelude to launching a small study in healthy volunteers."

### Producing suitable vaccine could take years

Commercial rights to the live attenuated vaccines developed by Desrosiers are owned by Therion Biologics, a Massachusetts-based biotechnology company. According to Dennis Panicali, the company's president, Therion is still uncertain as to whether the FDA would

approve such a trial and, if so, what specific requirements would be needed. In order to clarify these issues, the company is preparing a plan that it will submit to the agency by January, 1998. The plan will outline how the company could produce a live attenuated vaccine suitable for human testing.

As Panicali explains, a live HIV vaccine must be grown in laboratory cultures containing well-characterized living cells. The only feasible approach to growing large amounts of HIV consistently is to use "transformed" human cell lines. In the past, the FDA has been reluctant to

approve the use of these transformed T-cell lines to develop human vaccines. However, according to Panicali, this policy is currently under review.

Another option is to use infectious DNA clones, as the Macfarlane Burnet Centre in

Australia is proposing. While Panicali notes that there is no assurance that the full length DNA clones can actually infect people, a number of researchers, including Norman Letvin (also of the Harvard Medical School), have successfully infected monkeys with SIV DNA. Another question is whether the viral kinetics and immune response generated by an infectious HIV DNA clone would be sufficient to provide protection. IAVI is currently considering funding research to answer this question.

With all these uncertainties, Panicali suggests that, even in a very best case scenario, it would be at least two years before Therion could produce a vaccine suitable for human testing. He also noted that while IAPAC officials suggested they would go ahead with a trial, even without FDA approval, his company "would not, under any circumstances, produce a product for human testing without full FDA approval."

In addition to Therion, a North Carolina-based company, Biostratum, Inc. of Research Triangle, North Carolina, is reportedly developing a live attenuated HIV vaccine. According to J. Wesley Fox, vice-president of the company, Biostratum is developing a live attenuated HIV vaccine which contains novel deletions in "key genes, other than *nef*". Fox reports that the vaccine has protected primates against challenge with "an extremely pathogenic SHIV virus" developed by the company.

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**Safety concerns are unquestionably the greatest hurdle to human studies of live attenuated HIV vaccines.**

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## IAVI on Live Attenuated HIV Vaccines

IAVI has strongly committed itself to supporting research on live attenuated SIV and HIV vaccines. In October, 1996, the Initiative's board of directors approved an initial plan, developed by its scientific director and scientific advisory committee (SAC), to fund research and development in two key scientific areas that have not received adequate attention: 1) development of HIV DNA vaccines and 2) safety studies of live attenuated SIV and HIV vaccines. Specifically, in the area of live attenuated vaccines, IAVI will fund projects that can comprehensively address the key safety concerns associated with these vaccines. Two awards in this area will be announced shortly.

IAVI's scientific program seeks to fill key gaps in existing scientific efforts, particularly in accelerating applied research and development efforts. The Initiative does not conduct research itself, but rather provides funding to companies and research institutions that are best qualified to do so. As its funding stream increases, IAVI plans to expand its focus to other gaps in HIV vaccine development.

countries to do this for us," he told reporters. According to Prasert, more than 800,000 Thais are currently infected with HIV.

### Asian HIV cases to overtake Africa

At a keynote address to the congress, Peter Piot, executive director of UNAIDS (and a member of IAVI's board of directors), pointed out that Asia would soon overtake Africa as the center of the AIDS pandemic. He estimated that up to seven million Asians may currently be HIV-infected, and that at current rates of increase, this figure would double to 14 million by the year 2000. At that point, Asia would surpass sub-Saharan Africa in terms of the total number of HIV-infected individuals.

Regionally, the epidemic is focused in India, with between three and five million people living with HIV, followed by Thailand.

However, HIV is also spreading rapidly in other parts of the region, with a massive economic impact. By the year 2005, Piot estimated that Indonesia would be spending more than a third of its health budget on AIDS treatment. Cambodia could also face huge economic burdens. "In 10 years' time, there may be 200,000 AIDS cases and over 180,000 deaths [in Cambodia], generating a total loss of US\$2.8 billion," he said. Johnston reiterated this point, noting that a fraction of that figure could significantly transform the current HIV vaccine pipeline.

According to a report released by the Monitoring AIDS Pandemic (MAP) network, HIV is spreading rapidly in the opium-producing Golden Triangle. The people of this region, which includes parts of Myanmar (formerly Burma), Thailand and Laos, are at high risk for HIV infection. The epidemic is also spreading rapidly to nearby areas in India, China and the Mekong delta in Cambodia and Vietnam, being facilitated by unsafe sex with commercial sex workers, injection drug use and increased population mobility, according to the MAP report.

### Concerns about HIV vaccine development

The best way to stop the epidemic in Asia and other parts of the world, according to IAVI president Seth Berkley, is the development of safe and effective HIV vaccines that can be used throughout the world. However, Berkley warned that a

lack of investment was hindering research and development efforts. "If we could show companies that there was a US\$1 billion market for a vaccine in the developing world, we would see very rapid vaccine development." At the meeting, Berkley proposed the creation of international vaccine development and vaccine purchase funds to overcome the pharmaceutical industry's perceived lack of a viable market for HIV vaccines.

Yichen Lu, of the Institute for International Vaccine Development, in Massachusetts (U.S.), also criticized the current disincentives to HIV vaccine development. "I have no doubt that if the HIV epidemic had occurred 20 years earlier, then we would have a vaccine by now," he declared. "Progress by industry has been delayed by regulatory disincentives and

liability issues, while public sector funders such as the U.S. National Institutes of Health (NIH) have been hindered by their own decision-making processes."

Lu painted a gloomy picture of the history of HIV vaccine development, noting that in ten years very few HIV candidates have progressed to Phase II clinical trials, in stark contrast to vaccines developed for other diseases. Nevertheless, a new wave of optimism amongst vaccine researchers holds out hope for the future. "There has been a dramatic change in the last two years...now many scientists believe that a candidate vaccine will be here in five to seven years," he

said. Lu also detected a shift in the position of U.S. public sector funders as well. "NIH may be moving into development. This might break the deadlock."

Overall, many of the researchers appeared to agree with John McNeil, of the U.S. Walter Reed Army Institute of Research (WRAIR), who stated that clinical trials of HIV vaccines are "the only way we will move forward." The WRAIR hopes to be able to initiate, under the leadership of Thai researchers, a multi-arm HIV vaccine efficacy trial within four years. ■

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*Up to 7 million Asians  
may now be infected  
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## Merck Gives Emini Responsibility for Vaccine Research; Chiron Hires Liu to Head Its Effort

by David Gold

With increasing attention focused on the role of private industry in HIV vaccine research and development, two major companies recently announced key changes in their vaccine programs. These changes may have a significant impact on overall development efforts.

In May of this year, Merck & Co. disclosed that Emilio Emini, head of the company's highly successful HIV protease inhibitor program, would oversee all vaccine research at Merck. At the same time, a number of reports suggested that the pharmaceutical giant has decided to devote additional corporate resources and attention to its HIV vaccine program.

Just months later, in September, Chiron Corp., the U.S.-based biotechnology company, announced that it had hired Margaret Liu, former head of Merck's DNA vaccine program, to lead the company's overall vaccine research efforts.

Merck, which is developing DNA vaccines for a broad range of pathogens, including influenza, tuberculosis and HIV, has been tight-lipped about its HIV vaccine program. But publication of data in the Proceedings of the National Academy of Sciences, USA (PNAS, Letvin N, et al. 94:9378-9384; August, 1997) and presentations by company officials at scientific conferences and congressional hearings have shed considerably more light on Merck's program. The new information provides a picture of the company's pre-clinical efforts to develop an AIDS vaccine.

For some time, observers had believed that Merck's HIV DNA vaccine efforts would play a secondary role to other research efforts at the company, including the influenza DNA vaccine program. However, reports of disappointing results in a Phase I study of an influenza vac-

cine, an increased understanding of HIV pathogenesis and greater public attention to the need for an HIV vaccine all may have influenced Merck's decision to make HIV vaccine development a higher priority.

### DNA Vaccines

DNA vaccines are created by inserting one or more genes from a pathogen into a piece of DNA, which acts as a vector. The genetic material can then be injected directly into muscle tissue. (Other types of administration are also being studied.) Merck's DNA effort is based on a licensing agreement with Vical, a San Diego-based biotechnology company.

In animal studies, DNA vaccines have demonstrated the ability to induce potent cytotoxic lymphocyte (CTL) immune responses. However, to date, neutralizing antibodies generated by the vaccines appear to be relatively weak. Because of this, one strategy being pursued by a number of research teams, including Merck's, is to vaccinate with DNA and then boost with an HIV envelope protein that can induce high levels of neutralizing antibodies.

So far, the only company to initiate human studies of an HIV DNA vaccine is Apollon, a U.S.-based biotechnology company (see IAVI Report, vol.2, no.1).

### New Data Published

In the paper published in PNAS, researchers described a pilot study in which two macaque monkeys were given multiple immunizations of a DNA vaccine encoding envelope (HIV DNA) plus an HIV envelope protein boost (gp160). In total, the animals were given 9 injections of 1ug and 3 injections of 2ug of HIV DNA. Other macaques were given only

the gp160 or blank DNA. All of the monkeys were then challenged intravenously. At 28 weeks after challenge, both monkeys given the

HIV DNA plus gp160 were completely protected and had no detectable virus. On the other hand, all the control animals (receiving only blank DNA or gp160) became infected with measurable levels of virus.

At the Conference on Advances in AIDS Vaccines in May, Margaret Liu presented data on Merck's HIV DNA vac-

cine program (see IAVI Report, vol.2, no.2). She reported that the protection demonstrated in the pilot study suggests that "DNA immunization warrants active investigation." However, Liu cautioned that "other vaccine regimens, including monomeric gp120 and a canary pox prime boost combination, have also protected against a non-pathogenic SHIV challenge in monkeys."

### Development Plans

Merck is now initiating comprehensive animal studies to determine which DNA construct and boost will have the greatest likelihood of providing protection. The monkeys will be challenged with SHIV 89.6, a pathogenic virus that replicates quickly and causes rapid CD4 decline. One key question is how soon the company will move into Phase I human studies. Such studies would enable Merck researchers to obtain immunogenicity data in humans and compare it to what was seen in monkeys. Sources within the company suggest that Merck is laying the groundwork so that if a regimen is ready to go into human studies, the infrastructure will be ready.

In June, Gordon Douglas, president of Merck Vaccines (and a member of IAVI's board of directors), told the Congressional Task Force on International HIV/AIDS that, although the company's HIV vaccine effort is still in the pre-clinical stage, "we are committed to pursue an

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*Until Liu's appointment,*

*observers had been unsure of*

*Chiron's continued willingness*

*to invest in HIV vaccine*

*development.*

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Biostratum, which is working with researchers at the University of Kansas Medical Center, hopes to be able to test its vaccine in "a high risk human population at some point."

### Australian plans move ahead

While press attention has focused on efforts to launch a trial of the delta-4 vaccine in the U.S., researchers at Macfarlane Burnet Centre may actually be farther along in preparing for a human study of a live HIV vaccine. The Australian team, led by John Mills, is pursuing a different strategy than the U.S. researchers. It is attempting to produce a live vaccine that mimics an apparently weakened HIV strain found in a group of long-term non-progressors who became infected from a common blood donor. As was noted, the vaccine will be produced from infectious DNA clones capable of causing infection rather than the live virus that IAPAC is proposing. Mills believes that infectious DNA will be less expensive to produce, store and administer than live attenuated HIV. In an interview with the *IAVI Report* (see page 9), he suggests that, if all goes well, human trials could begin within 18 months.

### Overall outlook

Although most AIDS researchers have expressed admiration for the potential courage of the IAPAC volunteers, many appear to agree with Fauci and Bloom that it is too early to test a live attenuated HIV vaccine in humans.

Safety concerns are unquestionably the greatest hurdle to human studies of live attenuated HIV vaccines. Mark Grabowsky, who oversees Phase I and Phase II clinical safety trials of HIV vaccines at NIAID and attended the NIH meeting, believes that there is not yet enough evidence to suggest that the vaccines are safe.

However, Charles Farthing, a Los Angeles physician and IAPAC member who has volunteered for the trial, says "it is wrong to require an AIDS vaccine to meet U.S. safety and efficacy standards when 8,500 individuals are infected with HIV every day around the world." Given the enormity of the crisis, states Farthing, "further delays are unethical." Nevertheless, he recognizes that "our willingness to test the vaccine on ourselves is useless without the support of the decision makers in the U.S., the U.N., the scientific community and the biotechnology companies." ■

## Letters to the Editor

To the Editor:

As a scientist experienced in vaccine clinical trials, and now preparing for possible future efficacy trials of vaccines against HIV, I was fascinated by the IAVI Report's interview with David Baltimore (vol. 2, no. 2). I have shared his puzzlement about the origins of the animosity between the empirical and basic science research camps involved in HIV vaccine development, which I believe is due to a few bad apples in the extremes of each camp operating under erroneous epistemological assumptions about how their opposites work. Basic scientists seem to view empiricists as shotgunners wanting to try anything no matter what the rationale while empiricists seem to view basic scientists only as theorists sitting on their bums thinking while the world is overrun with HIV.

The formal definition of empiricism may shed some light on the problem. According to the current edition of "The New Shorter Oxford English Dictionary on Historical Principles", empiricism is "based on, guided by, or employing observation and experiment rather than theory ... used because it works, or is believed to." Using this definition, even theory-based, basic scientific research must be fundamentally empirical, since the eventual proof of every theory relies on experiment. But centuries ago, "empiricism" took on a specifically derogatory meaning as the practice of "medicine without scientific knowledge" and "ignorant, unscientific practice, quackery", losing its experimental aspect. Unfortunately, some empiricists seem to reinforce these negative implications by applying pressure to test vaccine concepts with the advancing epidemic, rather than scientific arguments, as their primary rationale.

Dr. Baltimore is, of course, right on target regarding the need for vaccine plausibility. But our problem is in deciding how plausible a vaccine concept is and whether it is plausible enough to justify launching efficacy trials. There, clearly, will be differences of opinion in making this judgment. But whatever we do, we better have good reasons, hopefully developed through consensus.

Dr. Cladd Stevens  
Laboratory of Epidemiology  
New York Blood Center  
New York, United States

To the Editor,

I was intrigued by David Baltimore's assertion that public money should not be invested in an empirical approach to HIV vaccine development since "this approach doesn't give you anything else in science...why should it give you an AIDS vaccine?" Instead of empiricism, I prefer to use the term "pragmatic", by which I mean taking something that works and improving it.

The spirit of pragmatism has pervaded vaccine development since its very inception. Neither Jenner nor Pasteur even knew what a virus was and yet they developed vaccines against smallpox and rabies. I do not begrudge scientists their fair share of public funding, but if it were stipulated that the only groups eligible for funding were those that have actually demonstrated protection in a relevant model in a way that would be acceptable for human use, how much of the work currently funded by the various AIDS vaccine initiatives would still be supported?

Dr. David Davis  
Institute of Tropical Medicine  
Antwerp, Belgium

# Making the Case for the Live Attenuated Approach: An Interview with Ronald Desrosiers

Ronald Desrosiers, Ph.D. is a professor of microbiology and molecular genetics at Harvard Medical School and chair of the microbiology division at the New England Regional Primate Center. In 1992, Desrosiers published the first data showing that a live attenuated SIV vaccine could protect monkeys against large doses of pathogenic SIV. Since that time, he has shown that additional attenuation of SIV could provide similar protection. Desrosiers has become increasingly vocal in advocating for the development and testing of live attenuated HIV vaccines. Yet even those who disagree with him acknowledge that the Harvard researcher is a top-notch scientist whose lab has produced important findings in the area of AIDS vaccine research.

**IAVI REPORT: Were you surprised that the proposed human study of a live attenuated HIV vaccine generated so much publicity?**

**DESROSIERS:** Not really. My experience has been that the topic engenders acute interest and differences of opinion. The issues are difficult, with strong sentiments for and against human trials.

**IAVI REPORT: Why do you believe that a human study is warranted?**

**DESROSIERS:** I personally don't have much hope that any other HIV vaccine approach is going to be effective. Yet a live attenuated vaccine has a good chance of being highly effective, relatively safe, and cheap to produce. There is ample evidence for safety, both from the rare cases of naturally infected humans and from SIV/monkey studies. So I think it is reasonable to plan for small scale safety trials of a live attenuated HIV vaccine.

**IAVI REPORT: What live vaccine would you suggest be tested in humans?**

**DESROSIERS:** For initial safety trials, we should make the virus more attenuated than it need be to ensure that there are no safety problems in the initial volunteers. So I suggest a vaccine that is near the extreme end of the attenuation scale, yet still infectious. My feeling is that a strain missing *nef*, *vpr*, *vpu* and the binding site for the transcription factor NF[ $\kappa$ ]B would be appropriate.

**IAVI REPORT: Does that vaccine protect monkeys?**

**DESROSIERS:** We have not tested this specific vaccine but we have tested one that is even less attenuated and it protects

monkeys against mucosal challenge. We have not published this yet.

**IAVI REPORT: At least four labs now have monkeys that developed immune suppression from live attenuated vaccines. What do you say to those who suggest it would be unsafe to test such vaccines in humans?**

**DESROSIERS:** Well, there are clearly some points of agreement. Everyone agrees that: 1) delta-*nef* (SIV with the *nef* gene deleted) and delta-3 (SIV with *nef* and two other genes deleted) are attenuated (weakened) relative to wild type virus; and 2) that the animals with higher viral load and evidence of disease progression have been a small minority — in our case, 3 of 45 animals and at the Aaron Diamond Center, 1 of 20. The numbers are low, but they are real.

So a number of points need to be considered. To begin with, while studying SIV mutants in monkeys is informative and should continue, the most relevant safety data are the rare humans found to be infected with *nef*-deleted forms of HIV. We described one in *The New England Journal of Medicine* in 1995 and an Australian group has described eight such individuals infected by a common blood donor (see interview with John Mills, page 9). These individuals have had low viral loads

and stable CD4 counts for more than 13 years from HIV with only a single *nef*-gene deletion.

Secondly, I have not been advocating delta-*nef* or even delta-3 as a vaccine for quite some time. The strains that should be considered are even further down on the attenuation scale and thus much less likely to cause adverse events.

Moreover, it is unrealistic to expect any live attenuated vaccine to be absolutely, 100% safe. Every live vaccine used in people has some adverse events associated with it. For example, the live polio vaccine is associated with a very small number of paralytic poliomyelitis cases. But society accepts this risk because of the overall benefits of the vaccine. Similarly, the likelihood of adverse events from an HIV vaccine must be weighed against the frequency of new infections and disease in a target population.

And finally, a relatively new development in support of going forward with live attenuated

vaccine trials is the availability of highly effective antiretroviral therapy. So, in the unlikely event that some volunteers develop viral loads in an uncomfortable range, highly effective drugs are available.

**IAVI REPORT: In the Australian cohort, the *nef* deletion appears to be getting larger over time.**

**DESROSIERS:** This cohort is really a remarkable finding. In that strain of HIV, the *nef* chain overlaps the LTR region, so there's a portion that is uniquely *nef* and the rest is

*nef*-LTR overlap. In the monkeys vaccinated with delta-*nef* and in the one individual we studied, the deletion was only in the *nef* gene.

But over time, the virus loses the rest of the *nef* coding sequence that overlaps the LTR. Since the virus doesn't have a functional *nef* gene, it apparently doesn't need those extra sequences any more. And the longer you go, the more the *nef*-LTR overlap is gone. We've said this in the literature several times.

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*I personally don't have much hope that any other approach (besides a live attenuated vaccine) is going to be effective.*

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**IAVI REPORT:** You attended a meeting with NIH officials about the proposed human studies (see article, page 1). What was your reaction to the meeting?

**DESROSIERS:** The attitude and response of NIH people towards the live attenuated approach was more supportive than I've ever seen. But nonetheless, I had the impression that, at the end of the day, the NIH people felt they had done their duty by listening and providing advice and now could go home and forget the issue.

**IAVI REPORT:** Why do you think some people take that position?

**DESROSIERS:** The issue is very difficult to deal with. There are no clear cut answers, and to come out in favor of going forward with a live attenuated vaccine is a very bold, risky move and one that most scientists don't want to deal with.

**IAVI REPORT:** Bottom line, do you think there are going to be human trials of a live attenuated HIV vaccine within the next two years?

**DESROSIERS:** If you asked me that six months ago I would have said "Not in my lifetime." But Charles Farthing, the physician who has advocated the human studies, totally independently of me I might add, has really stirred things up. He is a likable, caring human being and people are tending to listen to him. But if I had to bet money, I think it is still pretty unlikely.

**IAVI REPORT:** Should the first human trials take place in the industrialized countries or in the developing world?

**DESROSIERS:** Ideally, an initial small scale safety trial should take place in the United States. But if an appropriate institution in another country were to decide that this is something they want to try, I think we should be there to help them. But that is their decision.

**IAVI REPORT:** Therion Biologics owns the rights to the live attenuated vaccines you developed, but until very recently the company's interest in this approach seemed dead. Why is this?

**DESROSIERS:** It is important to realize that Therion is a very small company without much money. And trying to get FDA approval for a live attenuated HIV vaccine is going to

be a long, arduous and expensive process that is not easy for a small company to do. As I understand, the company has had discussions with the FDA about product development and manufacturing issues, but these are not very far advanced.

**IAVI REPORT:** What other HIV vaccine research is your lab working on?

**DESROSIERS:** We are looking at ways to enhance neutralizing antibody responses to the HIV envelope by addressing an issue that has been around for a while but for which

few meaningful experiments have been done, that is the role of carbohydrates on the envelope of the virus. We have been getting some very encouraging results suggesting that altering the carbohydrate composition of the envelope can dramatically enhance neutralizing antibody responses.

We are also studying whether we can generate the protection one gets with live attenuated vaccines by using a herpes virus vector; since the immune responses to herpes viruses can persist for the lifetime of a host. We don't have anything of promise yet, but we are working with David Knight and Jae June at Harvard in trying to construct and test herpes virus recombinants that express SIV antigens.

**IAVI REPORT:** What immune response do you believe is protecting most of the monkeys given live attenuated vaccines?

**DESROSIERS:** I believe that it is immune-

mediated and not some sort of interference phenomenon. We have evolved two arms of the immune system (cellular and humoral) for good reason, and it is likely that both arms of the immune system contribute to the protection. It is unlikely that one simple factor is solely responsible for the protection. Instead, I suspect it is a combination of varying types of immune responses.

**IAVI REPORT:** The only HIV vaccine approach that is attracting significant private capital is HIV DNA vaccines. Where do you see this approach?

**DESROSIERS:** DNA vaccines are very promising and I'm anxious to see the results of vaccine challenge experiments in monkeys. However, no one has yet used a DNA vaccine to protect against pathogenic SIV. We all know, from a vast array of studies, that it is relatively easy to get vaccine protection in monkeys using nonpathogenic, easy-to-neutralize strains of virus.

But it is very difficult to achieve protection, against disease-causing, difficult-to-neutralize strains that are representative of natural primary isolates of HIV. I could be very excited about the DNA approach if such a successful vaccine protection could be demonstrated.

**IAVI REPORT:** From your perspective, in the overall efforts to develop an AIDS vaccine, what should we be doing differently?

**DESROSIERS:** I agree that we need to pursue many vaccine approaches, compare them and eventually sort out which approach, if any, can best protect people against AIDS. But it is my belief that the live attenuated approach can make a real difference in the world, particularly in the developing countries that are being devastated by this epidemic. It can be effective, safe and inexpensive. What is lacking is a real charismatic, visible leader who is going to take a risk and get behind the approach. Someone like a Sabin, a Salk or a Jenner, who is willing to take criticism and move things forward, could have a huge impact. ■

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*We have evolved two arms of the immune system for a good reason. Both arms probably contribute to the protection seen in monkeys given the live attenuated vaccines.*

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# VACCINE BRIEFS

## **Uncertainties About Search for Director of NIH Vaccine Center**

While a search committee narrows its list of candidates for director of the new NIH Vaccine Research Center (VRC), growing uncertainties about the position may be deterring some highly qualified candidates from pursuing the post. These uncertainties, according to a number of sources, involve: 1) the scope of the position's authority; 2) who the position would report to; 3) the amount of resources that the position would actually control; and 4) whether the center would be competing with existing HIV vaccine programs at NIAID. Concerned about the situation, a group of influential researchers reportedly suggested to David Baltimore, chair of the NIH AIDS Vaccine Research Advisory Committee, that the new position should report directly to the head of the NIH, Harold Varmus. However, both Baltimore and Varmus appear to believe that the position should report to the leaders of the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID). Most disconcerting, according to some sources, is the possibility that the position may, in effect, end up reporting to the directors of intramural research at both institutes.

"The real pity," says one insider, "is that after seeing the reporting structure and how few resources the position will really control, what qualified person would take the job?" Another leading researcher, who was asked to apply for the position but declined, agrees, noting that the actual job description is far more limited in scope than had been suggested at the time of the announcement.

To date, the search committee has met only once, narrowing down the applications to 30 and then 15 candidates. At a planned November meeting, the committee hopes to select eight individuals to interview. It is expected that three names will then be presented to Varmus, who will make the ultimate selection. The NIH director is given credit by many for attracting a number of first-rate scientific leaders to the NIH. However, the failure to attract a well-respected, outside researcher for this high-profile position would be a blow to efforts to invigorate the NIH's AIDS vaccine program.

The VRC was first announced by U.S. President Bill Clinton in May, when he called for development of an AIDS vaccine by 2007. In an indication of the strong support that exists for the center, the U.S. Congress recently mandated that US\$26.1 million of next year's NIH budget be used for construction of facilities for the center.

## **Innovation Grants Awarded**

The NIH has awarded Innovation Grants in basic HIV vaccine research to 58 recipients. The grants will total US\$13.1 million during the first year of the program, with three of the awards given to non-U.S.-based research teams. A number of research centers received multiple awards, with the Aaron Diamond AIDS Research Center receiving three grants and Johns Hopkins University, Southwest Medical Center, Tulane University, University of Colorado,

University of Wisconsin and Emory University all being awarded two grants each. NIH officials report that they plan to expand the Innovation Grant program by adding two new areas of funding in the near future.

## **Cuban HIV Vaccine Trial Starts**

Cuba's Centro de Ingenieria Genetica y Biotecnologia has initiated a Phase I study of a candidate HIV vaccine, TAB9, which is based on a recombinant proteins from different V3 regions. The study will enroll 24 uninfected individuals (A more comprehensive report on this trial will appear in the next issue of the IAVI Report.)

## **IAVI Appointments**

IAVI's Board of Directors has appointed Seth Berkley, M.D. to be president of IAVI and Lee Smith, former president of Levi Strauss International and former chair of the National Leadership Coalition on AIDS (U.S.), to serve as chair of the board. The appointments were announced following the board's recent meeting, which was held in September in New York City. Four new board members were also appointed: Michèle Barzach, former minister of health (France); Geeta Rao Gupta, president, International Center for Research on Women (Washington, D.C.); Jacques-Francois Martin, chairman, Parteurop, SA (France) and Shudo Yamazaki, director general, National Institute of Infectious Diseases (Japan).

## **New Vaccine Trials Launched in U.S.**

A number of new HIV vaccine trials have recently been initiated in the U.S. These include: 1) a Phase II "prime boost" study of Pasteur-Mérieux-Connaught's ALVAC vCP205 and Chiron's gp120 boost that will enroll 480 "high and low risk" individuals in 14 sites around the U.S. (AVEG 2020/HIVNET 014); 2) a Phase I trial of ALVAC vCP205 administered mucosally (AVEG 027); 3) a Phase I study of Apollon's new DNA vaccine which includes the HIV genes gag and pol (AVEG 031); 4) a Phase I study of Therion's vaccinia construct with env, gag and pol segments and VaxGen's gp120 boost (AVEG 014C); and 5) a Phase I study of Chiron's recombinant protein p24 vaccine (Creighton University, Omaha).

## **Regional HIV/AIDS Meetings**

Regional AIDS meetings are being held in three separate continents this year. In addition to the 4th International Congress on AIDS in Asia and the Pacific, which was held in Manila, Philippines on 25-29 October, 1997, the 5th Pan-American Conference on AIDS will be held in Lima, Peru on 3-6 December, 1997 and the 10th International Conference on STDs and AIDS in Africa will be held in Abidjan, Ivory Coast on 7-11 December, 1997. IAVI representatives will make presentations and hold media briefings at these meetings. The Initiative, working with UNAIDS and other groups, is working to insure that HIV vaccine issues are one of central issues discussed at these meetings. ■



# Developing an HIV Vaccine from a Cohort of Long-term Non-progressors: An Interview with John Mills

*John Mills, M.D. became director of the Macfarlane Burnet Centre for Medical Research in Fairfield, Australia in 1992. The center is Australia's premier virology research institute and has major programs in basic virology, HIV, hepatitis and respiratory viruses, along with an international program focused on public health and the prevention of viral diseases. In his current position, Mills is overseeing an effort to develop a live attenuated HIV vaccine based on a strain of HIV that has been found in a blood donor and cohort of blood product recipients from Sydney, Australia who have remained "long-term non-progressors" for up to 17 years. Before moving to Australia, Mills was the director of the infectious disease program at the University of California at San Francisco.*

**IAVI REPORT: Can you tell us about the Sydney cohort of non-progressors that you are working with?**

**MILLS:** The cohort is an extraordinarily serendipitous experiment of nature which was discovered by the New South Wales Red Cross Blood Bank while attempting to identify people infected with HIV as the result of transfusions given between 1981 and 1985.

It consists of one donor, a gay man who, we now believe, was infected in January, 1981 and eight individuals who received blood products from this donor and who have been followed for up to 17 years after infection. Of these nine individuals, three have died. One patient had severe lupus. And two died in their eighties, basically of old age, without any evidence of progressive HIV infection.

All these individuals have a defect in the virus, a large missing segment in the nef gene, which is one of the nonstructural genes that has an uncertain function, and rearrangements in what is called the long terminal repeat (LTR), which is basically the control system that regulates the virus's ability to replicate.

**IAVI REPORT: What are the viral load levels of these six people?**

**MILLS:** Three of the patients have undetectable levels of HIV and three have very low but detectable levels (up to about 2,000 to 3,000 cc/ml). None have been treated with anti-retroviral therapy.

**IAVI REPORT: For those with quantifiable levels of HIV, are these levels increasing?**

**MILLS:** They appear steady but we really only have data over the past couple of years on that. Unfortunately we didn't save plasma samples frozen at -70° or -300° C in the appropriate storage materials to do the plasma viral load studies retrospectively. But there's no evidence that they have been increasing.

**IAVI REPORT: And immunologically?**

**MILLS:** By a whole variety of parameters they have normal immune function, along with skin test reactivity and proliferation to a number of antigens and mitogens. They have normal CD4 counts, with relatively elevated CD8 counts which I think simply represents the fact that they have a chronic infection. By all criteria they would be considered healthy, asymptomatic, immunologically normal individuals.

**IAVI REPORT: What is the focus of your current work with the cohort?**

**MILLS:** There are a couple of things that we are trying to do. Obviously, we want to try to develop a vaccine from this virus. The second step is to see if we can make a drug which

antagonizes the action of the nef protein. We are pursuing this with an Australian pharmaceutical company. It's a long shot but we are on track and hope to have something interesting in a year or two.

The third area we're interested in is understanding why the deletions in nef and the rearrangements in the long terminal repeat segments have affected the replication capacity of the virus.

**IAVI REPORT: How do those deletions in the nef genes compare with the deletions that Desrosiers made in his live attenuated SIV vaccines?**

**MILLS:** They are quite different. The nef gene in SIV is quite different than the nef gene in HIV. While there is good reason to believe that they have a similar mechanism of action, the sequences are diverged by about 50%.

Also, the deletion that Desrosiers made in his SIV strain is in the portion of the nef gene which does not overlap the LTR region. In contrast, the deletion in the Sydney cohort is in the portion of the nef gene which overlaps the LTR region. Now whether these are functionally similar deletions is one of the

unknowns and a basic science question that we are trying to address.

But in both SIV and HIV, once you make a single deletion in the nef gene, it appears to enlarge. In other words, the virus says "I'm not making a nef gene, so I might as well get rid of the excess genetic baggage which represents the rest of the nef gene." That has happened in the Sydney cohort and in the monkeys infected with the attenuated SIV vaccine.

**IAVI REPORT: So the deletions in nef have gotten bigger over the years?**

**MILLS:** Yes. In one member of the cohort there has been a significant enlargement in the size of the deletions over a four year period. And while we don't have prospective data on other members of the cohort, we do have genetic and serologic evidence that the initial deletion in the virus which infected these

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patients in 1981 or 1984, was much smaller than the deletions now present.

Most significantly, we now have nine patients followed for up to 17 years where this deletion has not repaired itself and has clearly increased in size. This gives us a great deal of confidence that this is an irreparable genetic injury. In other words, there is no possibility that this virus is going to revert to wild type in the sense of somehow reconstructing the missing genetic material.

**IAVI REPORT: Do the size of the deletions correlate with levels of HIV?**

**MILLS:** Oddly enough, the answer is no. In fact, if anything it would appear to be the other way around. There are two recipients that have very different deletions. One has a fairly small deletion of only about 200 base pairs and the other one has a very large deletion of about 700 base pairs. Interestingly enough, the virus with the huge deletion replicates better than the one with the minimal deletion. Why this happens is still an enigma.

**IAVI REPORT: So where are you now in terms of trying to develop a vaccine?**

**MILLS:** We have made molecular clones from the cohort virus which are full length and infectious. If a live attenuated HIV vaccine strategy is going to be practical in developing countries, it will have to utilize the DNA construct approach.

**IAVI REPORT: Can you explain for the lay audience exactly what a DNA clone is?**

**MILLS:** When HIV replicates, it normally has genetic material which is RNA, or ribonucleic acid. After it enters cells, it uses a characteristic enzyme called reverse transcriptase to manufacture a double stranded DNA copy of its genetic material. And this DNA copy of the genetic material has been inserted into the host, (i.e., the patient's chromosomal material) during the replication cycle of the virus. So a DNA copy is actually inserted into your chromosome and stays there for as long as you remain infected.

Now it turns out that you can, using molecular biology, construct the same sort of DNA copy of the RNA genetic material in the laboratory and squirt that into a cell and initiate HIV infection just about as efficiently as actually using an HIV virus. And that is essentially the strategy of making an infectious molecular

clone. It is making a DNA replica of the genetic material of the virus and using it as a vaccine.

**IAVI REPORT: What is the advantage of using DNA clones instead of live virus?**

**MILLS:** To deliver a live HIV vaccine as HIV viruses would be very difficult. Manufacturing would be difficult and expensive, and shipping, storing and maintaining quality control could be complex. Live virus vaccines also require refrigeration, probably freezing and are difficult and dangerous to administer.

In contrast, an infectious DNA-based HIV vaccine would be easy and inexpensive to manufacture in any country and doesn't require refrigeration. It is also stable and probably easy to administer. This is the focus of the project that IAVI is considering funding in Australia, assessing the practicality of delivering a live attenuated HIV vaccine using a DNA based strategy. It is a very important funding project.

**IAVI REPORT: How far along are you in initiating these studies?**

**MILLS:** The animal facility, the resources, reagents and staff are in all place. We expect to start two experiments within the next couple of months. The first experiment will study whether you can infect monkeys using infectious SIV DNA. We are using wild type pathogenic virus, because there is more experience with that. We are also making an SIV strain which mimics, as far as is possible, the DNA in the cohort. We will then see whether the infections with the attenuated SIV DNA will protect against virulent SIV infection.

**IAVI REPORT: If everything works out the way you hope with these two studies, when will you be ready to do a human study?**

**MILLS:** That is the \$64 billion question. The scientific and medical issues can be addressed fairly concretely. But the regulatory, ethical and political issues are more complex. Two things need to be done, and both are underway. We

are doing a comprehensive reanalysis of all the data (immunologic, clinical and otherwise) on the cohort just to reassure ourselves that they do not have progressive HIV infection. That should be completed within the next couple of months. The second thing is making sure we have an infectious molecular clone that's been sequenced and characterized. We then need to produce a vaccine for humans manufactured using good manufacturing practices (GMP). And we've identified a subcontractor who can do that for a reasonable price.

Our feeling is that the initial human studies should be done in an industrialized country, preferably Australia. We have had meetings with the TEA, the equivalent of the U.S. Food & Drug Administration here. They have been very helpful, but we will have to go through the same hurdles that any other vaccine goes through.

Another issue is: who goes first? Clearly, even self-experimentation requires ethics committee oversight. Individual investigators can be just as crazy as patients. And the first people to receive a

live attenuated HIV vaccine should probably not be young and sexually active because this is an infectious agent with a risk of transmission to others. Because all these issues need to be considered carefully, we've made preliminary steps towards creating an ethics panel.

Our Phase I studies are going to be infectivity and early safety studies. We are not proposing to vaccinate people and then wait another 17 years. That experiment is already done. What we need to know is, is this virus infectious as DNA? How much is required to produce an infection? And most importantly, what are the early characteristics of this infection? There is some evidence from the SIV model that even with an attenuated virus, initial infection can be fairly brisk. An attenuated strain of HIV could produce some disease early on and we need to assess that.

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*In terms of human trials, even self-experimentation requires ethical oversight. Individual investigators can be just as crazy as patients.*

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**IAVI REPORT: Is it possible to conceive of a human study within 18 to 24 months?**

**MILLS:** Yes, absolutely. Manufacturing this product to GMP standards is going to take a couple of months. Other preclinical work, assuming funds are available, will also take a couple of months. But once the green light is turned on, I think it is going to happen relatively quickly.

**IAVI REPORT: Do you think it will be difficult attracting human volunteers?**

**MILLS:** No. The issue is making sure that the volunteers are ethically appropriate. Even with limited publicity, we've had many people volunteer without being asked.

**IAVI REPORT: What do you make of the fact that a few of the monkeys given live attenuated SIV are now showing signs of AIDS?**

**MILLS:** That is worrisome. But SIV is not HIV. The disease model with SIV is very different. And the nef genes of SIV and HIV are very different.

Some people think that any degree of HIV infection is a bad thing. Yet, there are countries where 25% of the population may be HIV infected by age 22. Fifty percent of these people will be dead within seven years, most of the remaining within four years after that.

So if an attenuated HIV strain bought people 20 years or 25 years and then perhaps caused disease in some proportion of those patients, what are the real social risks and benefits of that equation? Tough question to answer. But not too different than those raised with any vaccine program. And ultimately, the politics may be as important as the science.

**IAVI REPORT: Would you enter a trial of the vaccine you are working on?**

**MILLS:** That's a perfectly reasonable question and the answer is a qualified yes. I'm getting on in years and in a monogamous relationship. So if my partner agreed, it would be something I would consider.

**IAVI REPORT: Is your lab working on any other HIV vaccine research?**

**MILLS:** Yes, we are working on an avipox-based strategy which looks very promising. The vaccine has enough differences from Pasteur-Mérieux's avipox vaccines that we think it is unique. And we have some preliminary protection data already. ■

# Remembering Diana, Princess of Wales

by Derek Bodell

I first became aware of Princess Diana's commitment to people with AIDS when she visited New York. I had missed her visit in 1987 to the Middlesex Hospital in London to open the first AIDS ward in Britain, as I was in U.S. working with a project supporting families at risk for HIV.

Her Royal Highness The Princess of Wales, as she was then titled, not only

visited an AIDS ward but held a baby who was potentially HIV-positive and spoke easily to the child's HIV-infected mother. The repercussions were astounding. In the world's most powerful democracy, it took a visiting Royal dignitary, in her own right a product of the English

upper class, to highlight one of the biggest health and social issues of the century. The TV coverage was extensive; The New York Times dedicated its lead editorial to the issue and from that time on the Princess of Wales never looked back.

I believe that Princess Diana did not have a specific strategy about her visits, conversations or physical contact with people with HIV. In her eyes, it was natural and normal to touch people to demonstrate understanding and compassion. I think she was genuinely surprised by the response but began to realise the impact it had made.

In 1988, I returned to Britain and was present when she opened an AIDS Centre in North London. You could not help being struck by her natural and easy manner with everyone she met. A good deal of her time was spent in a private session, without cameras, talking to a man

in a wheelchair who had Kaposi's sarcoma lesions on his face.

Since 1995, when I became director of the National AIDS Trust, I have had the opportunity to work more directly with the Princess of Wales in her role as our Patron. A Patron for a charity in Britain is someone who is committed to the work of the Trust, takes an active interest in its

projects and helps to raise funds. Originally we were one of 129 charities for which Princess Diana was the Patron and it was a great privilege when she reduced that number to six and we were one of them.

In her work on AIDS she articulated her priorities as being

prevention, treatment and care and the search for a 'cure', an answer which led her to support the International AIDS Vaccine Initiative.

Princess Diana challenged prejudice and discrimination by giving her time and commitment to helping people. In our discussions, she stressed her desire to use the media attention to make people aware of issues or causes that needed to be highlighted. And that is what she did.

Diana, Princess of Wales, may not have been the usual form heroes take. But for many, her blend of affection, charm and ability to listen and understand spoke volumes to a world that seems to have lost these priorities. I will remember a beautiful, elegant woman with infectious laughter emanating from an impish sense of humour that nobody was safe from. Let us hope the legacy she has left us of her own caring values endures for many years to come. ■



*Derek Bodell is Director of the National AIDS Trust, IAVI's U.K. partner organization.*

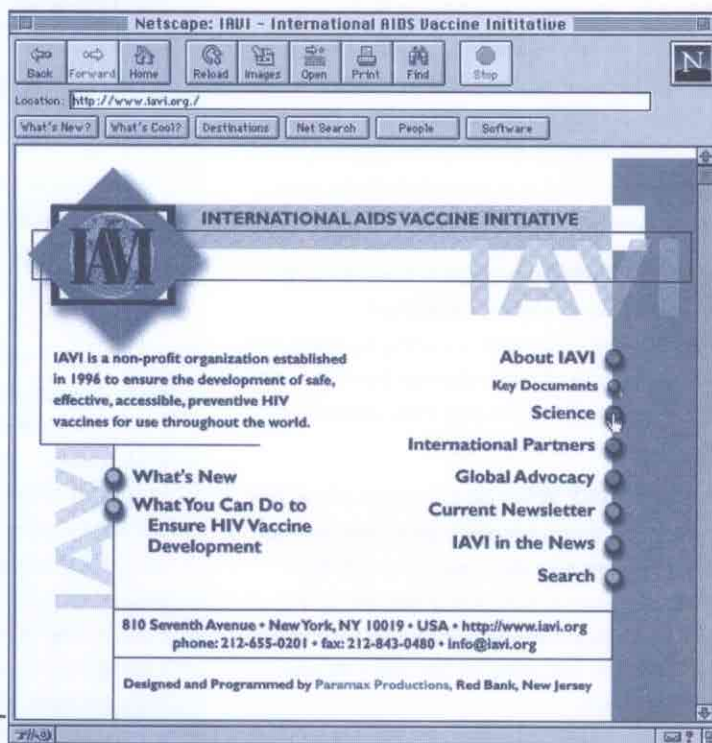
# IAVI Launches AIDS Vaccine Website

In October, IAVI launched a new HIV vaccine information center on the world-wide web. The site's address is: <http://www.iavi.org>.

In announcing the website, Seth Berkley, president of IAVI, noted that "we are especially heartened by the growth of the Internet in medium- and lower-income countries, where information on vaccine development has been difficult to access. Our hope is that 'www.iavi.org' will act as a focus for scientists, physicians, activists, the aid and development community, U.N. organizations and all those concerned about the rapid development of an HIV vaccine usable the world over," he said.

Key elements of the site include scientific information on HIV vaccine development, current and prior editions of the IAVI Report, a series of reports on HIV vaccine development published by IAVI and information on the initiative's scientific program, international partnerships, and global advocacy. The site was designed and produced by Paramax Productions, Inc.

Readers of the *IAVI Report*, which is currently distributed in 92 countries worldwide, can now send comments and opinions about the publication as well as subscription requests to: [iavireport@iavi.org](mailto:iavireport@iavi.org). General inquiries about IAVI should be directed to: [info@iavi.org](mailto:info@iavi.org). ■



## IAVI REPORT

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*WILL INDUSTRY MOVES BOOST...* continued from page 4  
HIV vaccine with as much vigor and passion as that which drove the discovery and development of our HIV protease inhibitor."

### Emini to Oversee Effort

Emini, who led Merck's successful protease development program, now becomes vice-president for antiviral and vaccine research at Merck. Earlier this year, he told *The Wall Street Journal* that "the tools still aren't there yet" to develop an effective HIV vaccine.

While these comments have led some to suggest that Emini may be overly cautious in terms of HIV vaccine research, the researcher told the *IAVI Report* that "the HIV vaccine program is now one of Merck's largest research efforts. We have a broad-based program led by first rate scientists. It is a well-funded, systematic and highly disciplined program that will try to address a number of key questions. Hopefully, we will be able to test candidate vaccines and also help fill in some of the holes in the overall basic research effort."

Emini had previously worked in the area of vaccine research at Merck. His proven track record in leading the company's HIV protease program through the difficult maze of AIDS drug development and licensing, and his reputation as a top-rate researcher, should prove extremely useful in overseeing the vaccine program. (Crixivan®, Merck's protease inhibitor, is expected to generate revenues of over US\$500 million per year.)

Merck's earlier efforts in the area of HIV vaccine development include an attempt to develop a sub-unit HIV vaccine based on the V3 loop in collaboration with Repligen, a U.S.-based biotechnology company. Merck also attempted to develop a monoclonal antibody to protect against HIV in collaboration with MedImmune, another U.S. biotechnology company.

### Liu to Head Chiron's Vaccine Program

Liu's decision to leave Merck to head vaccine research at Chiron was a surprise to many. She is considered to be one of the pioneers in the area of HIV DNA vaccines and is given credit for launching Merck's DNA vaccine program. Another reason for the surprise is that observers had been unsure about Chiron's continued willingness to invest significant research capital in HIV vaccine development. The company suffered a major disappointment when its recombinant herpes vaccine failed to show benefits in a large trial.

Liu, who will oversee all the company's U.S. vaccine research, told the *IAVI Report* that she moved to Chiron because "the position was the perfect opportunity for someone with my background. Chiron has an existing program with the ability to manufacture recombinant proteins and adjuvants. Although the company does not, as of yet, have a strong DNA vaccine program, it is doing important work in gene delivery systems." Chiron, she noted, "is fully committed to strengthening its HIV vaccine research program." ■