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IAVI REPORT

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Higher Profile for AIDS Vaccines at Retrovirus Conference

Interest in therapeutic vaccines could boost overall efforts, but reports of new infections in "resistant" sex workers highlight scientific challenges in protecting against HIV

by David Gold and Patricia Kahn

Throughout its seven-year history, the annual Conference on Human Retroviruses has focused primarily on HIV therapeutic research, and this year's meeting, held on 31 January-3 February 2000 in San Francisco, was no exception. But, this year it was also clear that AIDS vaccines are moving into a more prominent role at the closely-watched conference.

There were, to be sure, no dramatic new developments in the area of AIDS vaccines. Yet some key trends were evident, including: a growing understanding of the role of cellular immune responses in controlling HIV infection; new approaches to generating more potent antibodies; and a growing interest in testing candidate vaccines as therapeutic treatments for HIV-infected individuals (see article, page 3). The meeting also included presentations on HIV vaccines in development by Merck, Aventis Pasteur (formerly Pasteur-Mérieux-Connaught), Chiron and Wyeth Lederle Vaccines.

At the same time, two reports not directly related to vaccines provided sobering reminders that the task of generating long-term protection against HIV still presents significant scientific challenges.

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U.S. President Gathers Leaders to Push Vaccines

White House, Congress propose steps to encourage industry investment in AIDS, malaria and TB vaccines

by Victor Zonana

Pharmaceutical and biotech industry leaders pledged increased support for the development and deployment of affordable vaccines at a White House summit on vaccine development hosted by U.S. President Bill Clinton on 2 March 2000. The purpose of the unprecedented gathering was to build momentum in the private sector and to forge new partnerships among the participants, who included heads of United Nations organizations, foundations, leaders of the world's major vaccine producers, U.S. government officials, and vaccine and biotech experts.

Several of the CEOs used the occasion to describe new company initiatives on developing the most urgent vaccines, and most also announced donations of existing vaccines and medications for use in developing countries. These included one million doses of Hepatitis B vaccine from Merck, 10 million doses of Haemophilus influenza type-B vaccine from American Home Products, 50 million doses of polio vaccine from

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Infections in "resistant" Kenyan sex workers

The first of these, a poster from Rupert Kaul and colleagues at the University of Nairobi, described a disturbing development in the small minority of Kenyan sex workers who, despite intensive exposure to HIV, had remained seronegative for many years and were considered resistant to infection. But Kaul reported on six seroconversions in this group since 1996, all among women who had reduced their number of clients or stopped sex work for two months or longer. Comparison of the viral epitopes recognized by CTLs before and after seroconversion revealed that the infections occurred despite the presence of pre-existing HIV-specific CTLs (for up to 15-18 months prior to infection). There was no evidence that the infecting HIV strain contained viral "escape mutants" that could evade these CTLs.

These finding suggest that continuous exposure to antigen is necessary to maintain immunity in the "resistant" women. But their implications for HIV vaccines are not yet clear, since vaccine-induced protection might not be strictly comparable to the immunity induced upon exposure to infectious virus. (This work is discussed in an interview with Kaul's Oxford University colleague, Sarah Rowland-Jones, on page 10.)

Possible Superinfection with HIV

A second study highlighting the difficulties in generating immunity to HIV was reported in a late-breaker session by Jonathan Angel of Ottawa Hospital in Canada. Angel presented the case of an individual with a well-established but asymptomatic HIV infection who may have become "superinfected" with a new strain from a sexual partner with advanced disease. After the superinfection is thought to have occurred, the patient progressed rapidly to disease. While the report is based on preliminary data, it raises troubling questions about prospects for a vaccine: if an established HIV infection cannot generate sufficient immunity to protect against another strain of HIV, will a vaccine be able to induce protective responses? While infection with multiple strains of HIV is known to occur, the belief has been that the second infection must have occurred before the first HIV strain was well-established.

One study found that people with very low levels of HIV rarely transmit virus to their sexual partners, suggesting that vaccines which "blunt" viral load might reduce new infections.

Merck's HIV Vaccine Program Advances

John Shiver of Merck & Co. gave a progress report on his company's efforts to develop human codon-optimized HIV DNA vaccines. The optimized constructs showed significantly higher expression of HIV genes in human cells and generated far stronger CD8+ T-cell responses in small animals and monkeys than non-optimized DNA constructs. In December 1999, Merck began a Phase I trial of one of them, an HIV DNA candidate vaccine expressing *gag*. The trial will compare a range of doses and immunization regimens. Results could be available in the latter half of 2000. Shiver also discussed his company's efforts to develop standardized assays for measuring immune responses in vaccinated individuals.

Chiron's HIV Vaccine Program

Susan Barnett gave an overview of Chiron's HIV vaccine program, which is focused on enhancing HIV gene delivery (via DNA vaccines and the use of an alphavirus, Sindbis) and on producing protein vaccines made with new types of adjuvants. Chiron researchers are exploring several different approaches to increase the immunogenicity of DNA vaccines, including codon-optimizing the constructs for human cells. In addition, they are developing biodegradable microparticles (complexes of polylactide-co-glycolide, or PLG) that can present DNA vaccines in a way that dramatically increases expression of HIV genes. Initial studies have shown that the PLG microparticles generate 1000-fold higher antibody levels and 100-fold more CTLs in small animals. Barnett also reported that Sindbis vectors expressing HIV genes can target dendritic cells and generate potent CTLs and that Chiron's DNA *gag* constructs generated potent *gag*-specific CTLs and lymphoproliferative responses in macaques.

Chiron is also developing an oligomeric envelope protein (o-gp140) from primary HIV strains (with parts of the V2 loop deleted), with preliminary studies indicating that it generates antibodies capable of neutralizing at least some primary isolates. Earlier studies have suggested that deletion of the V2 loop makes the virus more sensitive to neutralization.

Wyeth's DNA Construct Tested with Canarypox Vector

Researchers from Wyeth Lederle Vaccines and NIAID's AIDS Vaccine Evaluation Group reported data on Phase I studies of the company's HIV *gag-pol* vaccine construct. Volunteers were immunized with different doses of the vaccine or a placebo. After four immunizations, none of the 31 immunized volunteers showed a measurable HIV-specific HIV-CTL response, but some volunteers did show HIV-specific T-helper response. Other volunteers are now receiving boosts with Aventis Pasteur's ALVAC vCP205 canarypox vector, making this the first prime boost study in humans focusing primarily on a cellular immune response. Previous prime boost combinations have included a viral vector with an envelope protein that generates mostly an antibody response. In total, 18 patients received an additional DNA immunization and two canarypox boosts. Using the ELISPOT assay, *gag*-specific responses were seen in 8% of patients before ALVAC boosts and 40% after the boosts. None of the vaccinees have shown tetramer-positive T-cells to date. Future tests will include the highest dose of DNA (3mg) and the ALVAC vCP1452. Nevertheless, the weak response seen in recipients of this DNA construct is disappointing.

CTL Responses to Viral Vector Vaccines

Norman Letvin of Harvard University presented recent data on several different vaccine approaches. An ALVAC canarypox vector (expressing SIV *gag-pol*) did not elicit "a large number of *gag*-specific CD8+ T-cells" in monkeys, but did show "some memory response." In total, 3 of 6 ALVAC-vaccinated monkeys had measurable SIV-specific CD8 + T-cells. But after challenge, the vaccinated monkeys showed no significant difference in their ability to control viral load compared with control

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Growing Interest in Therapeutic HIV Vaccines May Boost Preventive Vaccine Effort

by David Gold

One of the biggest stories coming out of this year's Retrovirus meeting is the growing interest in testing HIV vaccines together with potent anti-HIV drugs in already-infected individuals.

With mounting evidence that HIV-specific cellular immune responses may help control HIV infection, researchers are increasingly looking to test candidate vaccines as immune therapies. And with data from animal studies suggesting that some vaccines generate significant CD8+ T-cell responses, interest in therapeutic vaccines is moving into the mainstream.

"One can make excellent theoretical arguments as to why this might work," says Oxford University immunologist Andrew McMichael, who gave a plenary lecture on cellular immune responses to HIV at the conference. McMichael's team, with support from IAVI, has developed HIV DNA and MVA vaccines that are likely to move into Phase I studies in HIV-negative volunteers sometime this year. But McMichael told the *IAVI Report* that his team also plans to test these constructs as immune therapies in infected people.

What is particularly attractive about these studies is that researchers should know relatively quickly whether the vaccines help control HIV, since patients will likely be given a course of anti-HIV drugs plus a vaccine and then taken off therapy. They will then be monitored to see whether levels of HIV are kept in check.

This strategy has been studied in the SIV/monkey model by Genoveffa Franchini of the U.S National Cancer Institute. At the Retrovirus meeting, Franchini presented data on newly-infected monkeys treated with anti-HIV drugs and an NYVAC-SIV vaccine, and then taken off all therapy after 28 days. While there is a suggestion that the vaccinated monkeys are controlling SIV better than the unvaccinated ones, the difference has not reached statistical significance. (See *IAVI Report*, November-December 1999.)

In addition to Franchini's presentation, the Retrovirus meeting featured a late-breaker report on therapeutic vaccines by Marty Markowitz of the Aaron Diamond AIDS Research Center (ADARC). Markowitz showed that two newly-HIV-infected patients who were treated with HAART and a canarypox HIV vaccine (ALVAC vCP1452) seemed to control HIV when taken off therapy. No conclusions can be made from two patients, says ADARC head David Ho. But the goal in future studies, according to Ho, "is to see if by using immunotherapy we can pull people away from drugs."

A number of researchers attending the meeting also participated in a Think Tank on Therapeutic HIV Immunization led by University of California at San Francisco researcher Jay Levy. Sponsored by UCSF and Chiron Corporation, the think tank included presentations by Franchini, Ho, Chiron's Susan Barnett and Francis Gotch of the Chelsea and Westminster Hospital in London.

If they prove to be effective, therapeutic HIV vaccines would have a lucrative market in the world's industrialized countries. Manufacturers would surely make the case for high priced immunogens based on savings from patients going off expensive anti-HIV therapy for extended periods of time.

And, according to reports at the conference, long-term treatment with anti-HIV drugs may cause significant side-effects in some patients, most prominently a range of metabolic disorders. (A related topic at the meeting was a strategy being employed by a number of patients in an attempt to limit drug-related toxicities and stimulate immunity: the use of structured treatment interruptions.)

Proponents of therapeutic vaccines also suggest the possibility that patients in developing countries may be able to benefit from a cheaper, shorter course treatment of anti-HIV drugs if it is combined with an HIV vaccine.

Industry clearly senses an opportunity. One researcher at a leading pharmaceutical company told the *IAVI Report* that his company's marketing department has already conducted an analysis of the potential market and pricing options for therapeutic HIV vaccines. "This will help spur investment in our vaccine program, which is a very good thing," says the researcher. "But it's interesting that in all my years here, I have never once seen a market study for a preventive HIV vaccine."

Aventis Pasteur's Michel Klein reports that his company has already created a program to test a number of the company's candidate HIV vaccines as therapies. Aventis is currently conducting seven different therapeutic HIV vaccine trials.

Smaller biotechnology companies do not want to be left behind. Robert Johnston of AlphaVax reports that his company hopes to move its VEE vector-based HIV vaccine into HIV-negative volunteers sometime this year, and shortly after that in HIV-infected individuals. These companies know that in the lucrative but fiercely competitive AIDS drug market, being the first approved therapy in a particular class can confer long-lasting advantages.

And interest is not limited to industry. Giuseppe Panteleo, a researcher at the Hôpital Beaumont in Lausanne and a leader of EUROVAC (a European Union-funded consortium on HIV vaccines) told the *IAVI Report* that the consortium plans to test a number of immunogens, including MVA, NYVAC and DNA constructs, as both preventive and therapeutic immunogens.

To be sure, the usefulness of therapeutic HIV vaccines remains to be demonstrated. Only a small number of human studies have been started and no study – either in humans or in animals – has yet shown any clear benefits. Nevertheless, the race to establish a foothold in a potentially lucrative market just may encourage more investment – and some competition – in developing HIV vaccines.

These studies also may help answer some fundamental questions. "Current AIDS therapies enhance immune responses to everything but HIV," says UCSF's Jay Levy. "Why they don't bring back HIV-specific immune responses is one of the most interesting immunological questions we face. We haven't come up with an explanation, but if we immunize while on therapy, we may be able to bring back HIV immunity.

"Researchers will be able to study many of the preventive vaccines to see if they can also benefit those already infected," adds Levy, who co-discovered HIV. "It's an old idea that Jonas Salk raised years ago, but at that time we didn't have powerful drugs that dramatically reduce viral load and the prospect of vaccines that stimulate a good cellular immune response."

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animals. Officials of Aventis Pasteur, which produced the canarypox vectors, note that comparisons of their vector with other vaccines are difficult to make from Letvin's data since different immunization and challenge schedules were used.

Letvin also described the use of Interleukin-2 (IL-2), either as plasmid DNA or as protein, to augment the immune responses elicited by SIV-DNA vaccines. Immune responses generated by SIV-DNA vaccines with an IL-2 protein or IL-2-expressing plasmid were "significantly higher" than with DNA alone. The highest and most durable CTL response was with the DNA vaccine plus IL-2 plasmid given two days earlier. In the discussion, Letvin suggested that the IL-2 plasmid should also be able to enhance CTL response to viral vectors.

Aaron Diamond's Codon Optimized DNA

Researchers from Aaron Diamond AIDS Research Center (ADARC) reported on their own human-codon optimized HIV vaccine construct, which is based on a subtype C HIV strain. In lab studies, it showed more than 100-fold higher expression levels. ADARC researchers are now studying the construct in rhesus macaques.

Neutralizing Antibodies and Protection

The past year's resurgence of interest in HIV antibodies was also reflected at the meeting, where speakers addressed the potential of humoral immunity to protect against HIV and described efforts to create antigens that induce more potent antibody responses.

Carl Hanson of the California Department of Health Services described studies on antibody-mediated protection using a mouse monoclonal (called B4) against human cell surface HIV receptors, an approach which avoids the potential problem that immune responses to HIV may not work across diverse subtypes. B4 showed strong binding to surface-bound (but not soluble) CD4 receptors and enhanced binding to CCR5, yet displayed no signs of being cytotoxic or immunosuppressive. It also blocked replication of SIV, SHIV and primary HIV isolates from many clades, and neutralized HIV taken directly from patients. Most important, it protected SCID-Hu mice (a mutant strain which lacks a functional immune system) when given either just before or within 4 hours of challenge with HIV. Similarly, chimpanzees treated with high levels of B4 were protected from an IV challenge. Hanson also described the identification of a peptide that mimics the target site of B4 and which is now being developed as a candidate vaccine in collaboration with United Biomedical, Inc. of New York.

B4 was also tested as a therapeutic agent and found to dramatically lower viral load in highly viremic chimps. Further tests of its therapeutic potential in combination with HAART are planned.

John Mascola of the U.S. Army's Walter Reed Army Institute of Research presented his newly-published study showing that certain antibodies infused into female rhesus monkeys can protect against vaginal challenge with pathogenic SHIV. (*Nature Medicine*, February 2000). The strongest protection (4 out of 5 animals) was seen with a pooled mixture of IgG from several HIV-infected people plus two human IgG monoclonal antibodies previously shown to neutralize a broad spectrum of primary HIV isolates. (One monoclonal recognized a conserved region of gp41, the other a conformational epitope in the C3-V4 region of gp120.) The two monoclonals without the polyclonal IgG protected 2 out of 5 animals, while the anti-gp120 monoclonal alone protected 2 of 4. In all three cases, even animals that were not protected showed lower viral loads and higher CD4+ counts compared to controls.

The key question in translating these findings into vaccine strategies is whether a vaccine can induce and sustain protective levels of neutralizing antibodies, especially given the failure of candidate vaccines to neutralize primary isolates thus far. But Mascola emphasized that it took less antibody to protect the monkeys against mucosal challenge compared to IV challenge (although pre-treatment of animals with progesterone caused thinning of the vaginal surfaces and could have helped antibodies enter the mucosa). He also noted that the monoclonal antibody that generated partial protection by itself showed only "modest" neutralizing activity.

In a poster presentation, researchers led by Nancy Haigwood of the University of Washington also showed that high levels of antibodies can protect against SIV, even after infection. Haigwood's team gave SIV-IG (purified IgG from SIV-infected, nonprogressing monkeys) to monkeys 1-14 days after intravenous infection with pathogenic SIV-E660. Overall, 6 of 9 SIVIG treated monkeys showed no CD4 decline, compared to only 1 of 5 control animals.

Peter Kim on the gp41 Fusion Region

Several labs reported work on potential strategies for inducing neutralizing antibodies. In a plenary talk, Peter Kim of the Massachusetts Institute of Technology described how his lab's structural studies on the HIV envelope protein led to identification of a key, highly conserved functional domain within gp41 that is an attractive target for HIV vaccines aimed at humoral immunity. The region is found deep within the molecule's core and normally exists as a 3-strand "coiled coil" or "superhelix", composed of three helical strands twisted around one another. By analogy to other viral proteins, Kim reasoned that this region helps HIV enter host cells by acting as a spring which releases when HIV binds to its cellular receptor, thereby moving the fusion region of envelope protein into position for fusing with the cell membrane. This notion now has experimental support, since certain peptides corresponding to the fusion region turn out to be potent inhibitors of HIV entry – a finding that has led to the development of therapeutic peptides, currently in clinical trial. Kim also speculated that the intermediate created by the fusion region's movement could be the structure against which University of Montana researcher Jack Nunberg generated neutralizing antibodies in his widely reported research last year (see *IAVI Report*, July-August 1999). Kim's lab is now attempting to make antibodies against the relevant peptides.

Making Native Envelope Antigens

Another attempt to create envelope antigens that induce neutralizing antibody was reported in a poster by John Moore's

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Moving IAVI's R&D Program Forward: An Interview with Wayne Koff

In 1999, Wayne Koff became IAVI's Vice President for Research & Development, assuming responsibility for overseeing the Initiative's overall scientific program. Koff first became involved in AIDS vaccine research after joining the U.S. National Institutes of Health (NIH) in 1986, eventually becoming chief of the agency's AIDS vaccine program. He then moved to the private sector, joining United Biomedical, Inc. where he was instrumental in launching clinical trials of a candidate HIV vaccine in China, Thailand, and Brazil, thus demonstrating the feasibility of testing AIDS vaccines in developing countries.

IAVI Report: Where is IAVI's vaccine research program now?

Koff: We are focused on moving the most promising candidate vaccines into clinical trials in developing countries and making sure the best of these progress to efficacy trials. Our goal is to identify innovative vaccine approaches that represent improvements over what is now in clinical trials, and drive them forward as fast as we can. One of our challenges is time. It can take years to get a vaccine concept into a clinical trial. We want to accelerate these timelines.

It's also been difficult to compare vaccine approaches. So we're trying to run parallel human trials and animal studies comparing different approaches. And weíre working to identify approaches that can be easily used in developing countries.

To date, the approaches weíre supporting focus on optimizing cellular immune responses, since cellular immunity is clearly important in controlling HIV. But since we also believe that effective neutralizing antibodies will be a critical component, we will start focusing on this area later this year.

With cellular responses, we're a lot better off than we were a few years ago. But we're still at square one in terms of generating antibodies that neutralize primary HIV isolates.

You have worked on AIDS vaccines in government, industry, and, now with IAVI. What can IAVI do that others can't?

In the public sector, particularly the NIH – the real strength is basic research. That's what they're good at. NIH is also quite effective at conducting large multi-center clinical trials. They have a long track record in working with larger companies on Phase IIII vaccine trials. Look at the pertussis trials.

Industry – especially the larger companies – has the resources and the know-how to take a concept out of basic research, make a product and move it into clinical trials. Now in diseases where the scientific feasibility and commercial market are clear, the public and private sectors are both engaged.

But with AIDS vaccines, there are substantial obstacles – scientific, commercial, and political. So there hasn't been much activity in the private sector, considering the magnitude of the problem. That's where IAVI can help jump-start the effort. So weíre trying to identify better approaches, bringing in teams of experts to speed up development and demonstrate feasibility, and thus really move these candidates forward.

We can also combine technologies to make a better vaccine. One example weíre considering is taking an alphavirus vector expressing a DNA vaccine and putting it into a bacterial vector, which can be used for oral immunization.

What is the status of IAVI's vaccine development partnerships (VDPs)?

The VDP program is the heart of IAVI's R&D effort, since it links vaccine design labs in the industrialized world with clinical researchers in the developing world. In November 1998, IAVI decided to back Oxford researcher Andrew McMichael in developing a DNA and MVA prime boost combination. Andrew is an internationally recognized immunologist, particularly in the area of cytotoxic T-cells (CTLs). His group worked with Adrian Hill on the same approach for malaria and established a collaboration in Kenya, which IAVI is now assisting in preparing for clinical trials.

IAVI also funded a Venezuelan equine encephalitis replicon particle (VEE) developed by Robert Johnston's team at the University of North Carolina and AlphaVax Corporation. Their VEE approach, which has also been supported by the NIH and U.S. Department of Defense, has shown promising results against SIV in monkeys and in other animal models against influenza and Marburg. Alphavax is working with researchers in South Africa to prepare for clinical trials.

When will these approaches move into human trials?

The DNA/MVA approach should be in clinical trials by August 2000 at Oxford and three months later in Kenya – each component individually, and then together. It's a little more challenging to get the VEE vaccine into human trials, but Alphavax has made a lot of progress and we hope to start trials by the end of 2000. The immunogens focus on the HIV gag gene, although Oxford's vaccine also contains mini-genes reflecting CTL epitopes matched to common Kenyan HLA types.

What about using multi-gene constructs?

The plan for all IAVI-sponsored vaccines is to include multiple HIV genes. Both VDPs are working on second-generation vaccines. But there's a lot of value in getting into the clinic early to test the basic strategy. Getting new and improved concepts into clinical trials will be a major milestone for IAVI, and also test our trial infrastructure in developing countries.

Are there plans for new VDPs?

Yes. In August, IAVI's scientific advisory committee reviewed

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promising approaches that have particular advantages for developing countries. These included single-shot vaccines, orally administered vaccines and others.

All our vaccines are made from viruses circulating in the country where we plan to conduct initial trials. But our ultimate goal is to have a broad-based vaccine that is usable throughout the world.

Our newest VDP is an adeno-associated virus (AAV) vector, designed by Phil Johnson at Children's Research Institute of Columbus, Ohio, and being developed by Targeted Genetics Corporation. We plan to develop this approach for clinical trials in both Eastern and Southern Africa. AAV's key advantage is persistence of antigen, so a single-shot might be feasible. That would be very helpful in developing countries and it might offer long-term immunity. In preliminary studies in monkeys, a single shot of an AAV vector expressing SIV genes has done as well or better than all other vaccine approaches, except for live-attenuated vaccines.

The next VDP will use bacterial vectors, such as salmonella, as a delivery system for DNA vaccines. These vectors can be delivered orally, they target the mucosal system and they are cheap to produce. And the bacterial vector may require far less DNA. So you have all the advantages of an oral vaccine at far less cost.

Do you have any concerns about the safety of AAV, given the persistence of antigen?

Wild-type AAV has never been known to cause human disease, and recombinant AAV vectors have an impeccable track record of safety. They've already been used in Phase I gene therapy trials, so, this will not be the first AAV trial.

There are two key issues in using AAV as a vaccine vector, and we are working with FDA and other regulatory authorities to address them. First, to achieve a persistent infection, the vector is going to integrate into the genome, which makes it important to show where in the body the vector is going. So the vaccine manufacturer will conduct biodistribution studies in animals to track the distribution of AAV following immunization. Second, the continuous cell line which AAV is grown in will be fully characterized to eliminate the chance that DNA cells are carried over into the vaccine. We have already begun a series of discussions with U.S. Food and Drug Administration (FDA) on protocols for product development, and these discussions are going on in the spirit of trying to move expeditiously, and carefully, into Phase I trials. In all the species that AAV has been studied, there haven't been any significant adverse reactions. So we're not anticipating any problems.

Are you optimistic about overall prospects for an AIDS vaccine?

Yes. Based on the efficacy of live-attenuated vaccines in the SIV-monkey system, and the capacity of the human immune system to control HIV for at least several years, I'm convinced that a safe and effective AIDS vaccine will be developed.

But there's a fine line between the optimist and the fool, so we must try to anticipate the unexpected. We now know a lot more about what we're trying to achieve with an AIDS vaccine. But we'd be better off if we knew why live-attenuated

IAVI Announces HIV Vaccine Project Aimed at Generating Long-Term Immunity

by Patricia Kahn

On 15 February 2000, IAVI announced the launch of a collaborative project to develop a candidate HIV vaccine based on a recombinant adeno-associated virus vector (rAAV). The approach could potentially lead to a single-shot vaccine with properties that make it well-suited for use in the developing world. Partners on the project are Philip Johnson of the Children's Hospital in Columbus, Ohio, whose lab designed the vector (initially for use in gene therapy) and developed the system used to produce it, and Targeted Genetics of Seattle, Washington, which commercialized the rAAV technology and will manufacture the vaccine. The project is IAVI's third Vaccine Development Partnership (VDP), a collaborative venture that brings together academic researchers, vaccine manufacturers and clinical researchers from developing countries where the vaccine trials will be conducted (in this case, Eastern Africa and/or South Africa). Like both of the earlier VDPs, this one includes an agreement with the manufacturer that vaccine (if it proves to be effective) will be made available at affordable prices in poor countries.

The key advantage of rAAV as a vaccine platform is its potential for inducing long-lived immune responses. This property stems from the fact that AAV – which often infects humans and other animals in nature, producing an asymptomatic infection – integrates into the chromosomes of its host and establishes a persistent presence. When AAV's two genes are replaced with DNA from HIV (or other foreign DNA), infected cells will contain integrated copies and continuously express the HIV protein(s).

Preclinical data in both small animals and monkeys support the idea that persistent expression translates into long-term immunity. Most telling were experiments in monkeys immunized with an rAAV-SIV vaccine containing either the SIVgp160 or gp140 gene, in which 5 out of 6 animals showed CD8+ T-cell responses that remained strong for up to 15 months following a single injection. In a separate experiment with the SIVgp160 vaccine, 10 of 11 monkeys showed measurable neutralizing antibody responses. That held true even for animals with low levels of pre-existing antibody to AAV, an important finding in view of the fact that AAV infection is common in humans.

The rAAV vaccine platform offers other advantages in

vaccines work in monkeys, and what immune correlates might be relevant in that system.

I think we'll need to generate effective, long-lasting antibody and cellular immune responses for an effective AIDS vaccine. We're now a lot better off on the cellular side than we were a few years ago, but we're still at square one in terms of neutralizing primary isolates of HIV.

And we need to get a few products through efficacy trials to begin to see where the bar is in terms of what is needed for protection. We can't answer these questions without such data.

If people think we can rely on three monkeys and thirty human volunteers to get real answers, they are mistaken.

Should the U.S. government fund an efficacy trial of the canarypox-based vaccines?

Yes. I don't think anybody thinks these vectors will be the perfect vaccine. And they may not even work at all. But to sit back and say, "In four or five years, we'll have something better, so don't test this now" is not something I agree with.

A key question to ask is: "what data do we need by 2005 that can bring us closer to a successful vaccine?" Then we need to set the wheels in motion to generate such data. IAVI can play a critical role in this effort, since it has the ability to move rapidly. Obtaining data on the level of efficacy achieved by a vaccine that generates HIV-specific CTLs – whether it be canarypox, DNA, MVA or VEE – would be a big step forward.

How would you approach developing constructs that generate potent neutralizing antibodies?

No vaccine now in clinical trials stimulates neutralizing antibodies against HIV strains transmitted in the real world (as compared to laboratory-adapted strains.) So IAVI has created a task force of leading international players chaired by Carl Hanson, with the goal of designing such immunogens. We need to think more broadly than we have in the past and I wouldn't rule out anything. People are worried about complex immunogens, such as host-cell antigens and viral proteins combined. I wouldn't worry about that. Instead, I would first try to achieve a consistent level of effective neutralizing antibody, and then ask: "is the immunogen safe and practical?"

Is there anything out there now that may induce potent neutralizing antibodies?

I see three interesting areas now. One, there are a few monoclonal antibodies directed against HIV's outer envelope glycoproteins that have shown some ability to stimulate neutralizing antibodies against primary isolates. Nobody has figured out how to make an antigen that can elicit these antibodies. And it probably won't be easy to work back from them, but a concerted effort must be considered.

Another approach is to make a more native envelope glycoprotein, either by cross-linking to achieve an oligomer, or by other strategies, such as deleting glycosylation sites. These constructs are now in small animal studies.

A third approach is to look at host cell antigens and at complexes between host cell and viral antigens. This area is

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terms of use in developing countries. Particles are highly stable and do not require refrigeration, which would greatly simplify transport and delivery of vaccine. Another plus is ease of large-scale manufacture, which is already well worked out using a cell line containing integrated rAAV that can easily be made to mass-produce the particles.

Johnson's lab will develop rAAV-HIV vaccines based on an HIV-1 subtype A strain from Uganda and a subtype C from South Africa, initially containing the *gag* gene and later to include *env* and possibly other genetic information from HIV. The subtype C constructs will contain the identical HIV genes as another vaccine product in development (based on the Venezuelan equine encephalitis vector) at AlphaVax Corp. in North Carolina under the auspices of another IAVI-sponsored VDP. This will facilitate head-to-head comparison of the two vaccine products in animal studies and clinical trials later on.

Alongside the vaccine development work, the new VDP will also focus on generating data to address the safety issues raised by an rAAV-based vaccine. This workplan was developed after consultation with the U.S. Food and Drug Administration (FDA) about what information they will need to consider approval for clinical trials and eventual licensure. The first issue pertains to the integration of rAAV into human chromosomes, which occurs at both a specific site (on chromosome 19) and randomly. Although the vector has already been administered to approximately 80 people without any detectable adverse effects, most of those who received it were participants in gene therapy trials for cystic fibrosis, in which vector was sprayed into the lungs (into cells that are eventually shed). Since a vaccine injected intramuscularly is likely to persist in the body indefinitely and settle into different tissues of the body than vector delivered by spray, biodistribution studies in animals will be carried out to examine this in detail. The key question is whether vector will migrate and then integrate into germline cells, which it does not seem to do in the animal studies done so far.

The other safety issue involves the use of an established human cell line as the "packaging" system to produce the rAAV particles. This type of cell substrate has not yet been approved for use in making vaccines, although the cell line-based production was approved for rAAV gene therapy trials. Work will focus on ways to thoroughly remove (and accurately measure) residual cellular DNA from the rAAV particle preparations, to eliminate the theoretical risk of introducing any harmful genetic material into the vaccine.

Although both the integration and cell line issues "break new regulatory ground for vaccines," says Wayne Koff, IAVI's vice president for research and development, he characterized discussions with the FDA so far as constructive and "in the spirit of trying to move carefully into Phase I trials. In all species where AAV has been studied, there haven't been any significant adverse reactions. So we're not anticipating problems," he said in an interview published here (see page 5).

Industry Insider

Vical's Stock Fluctuates, Merck Cautious

While biotechnology became the darling of Wall Street over the past six months (until a mid-March correction), few companies have seen as dramatic fluctuations in their stock price as Vical. The San Diego-based company, which licensed its rights to develop HIV DNA vaccines to Merck & Co., has seen its shares jump from $14 to a high of $69 on 17 February and then drop back to $27 by 21 March.

Merck began a Phase I trial of an HIV DNA candidate vaccine in December 1999. The trial is enrolling volunteers at a number of sites across the U.S. Despite the trial's launch, Merck officials appear to be quite cautious about the vaccine program's long-term outlook. "This is Year 15 in our effort to develop an HIV vaccine. I think we have (another) decade ahead of us," Adel Mahmoud, president of Merck Vaccines, told Reuters on 3 March. Laurence Hirsch of Merck Research Laboratories was even more pessimistic. "Unfortunately, there is a likelihood (that this) vaccine will fail," he was reported to have said.

Targeted Genetics Announces Partnership, Avigen Reports Promising AAV Data

Another biotechnology company, the Seattle-based Targeted Genetics Corp, announced a new partnership with IAVI and Children's Research Institute of Columbus to develop an HIV vaccine (see page 6). The announcement was made at the announced at the BIO Investors Conference on 16 February in New York. That same day, Targeted Genetics' stock price jumped 57%.

IAVI, which will fund preclinical development and Phase I studies of the vaccine, expects to invest more than US$6 million in the effort, provided that specific milestones are met. Targeted Genetics owns specific rights for production and use of adeno-associated virus (AAV) as a viral vector. In return for its investment, IAVI has secured rights to ensure that a successful vaccine will be distributed in developing countries at a reasonable price.

At the same time, researchers from Stanford University and Avigen, a California-based biotechnology company, reported in *Nature Genetics* (March 2000) that a gene therapy study using an AAV vector has shown promising results in three patients with hemophilia B. A serious bleeding disorder, hemophilia B is caused by a defective gene for a blood-clotting protein called Factor IX. The AAV vector was designed to deliver a healthy version of the Factor IX gene into the cells of their patients.

Progenics Reports Work on HIV Vaccines

In January, Progenics Pharmaceuticals reported that it has produced a construct that more closely mimics HIV's envelope glycoproteins, and, thus, according to the company, has the potential to generate antibodies capable of neutralizing real-life strains of HIV. (See also page 14.) The New York-based Progenics is working with a research team led by John Moore of the Aaron Diamond AIDS Research Center and is reportedly being considered for a large NIAID vaccine development grant. Progenics CEO Paul Maddon told the *IAVI Report* that his company plans to begin animal tests of the construct, and, is also considering running parallel studies in animals and humans. "We hope to demonstrate that immune responses generated by our construct are superior to that generated by the envelope constructs currently in human trials," he said. About half of Progenic's current R&D activities is related to HIV, the other half is focused on cancer. The company has a melonoma therapeutic vaccine currently in Phase III trials.

Margaret Liu Leaves Chiron

Margaret Liu, the well-respected head of Chiron Corp's HIV Vaccine Program, left the company in January. Liu reportedly had differences with some of Chiron's leadership about the future direction of the company's vaccine program.

U.S. vaccine advocates expressed concern about Liu's departure. "Margaret did a great job in expanding and broadening Chiron's HIV vaccine program," said Bill Snow of the U.S.-based AIDS Vaccine Advocacy Coalition. "We hope that the company continues these efforts," he added.

In other news, Chiron announced on 29 February that it had been granted two U.S. patents on the use of alphavirus replicons to deliver genes in vaccines for infectious diseases such as HIV and hepatitis C. The company's management, led by CEO Sean Lance, has begun to shed non-core operations, and is expected to announce some layoffs in the vaccine research program.

Cel-Sci "Matures" Out of HIV

The Virginia-based biotechnology company Cel-Sci is moving away from HIV vaccine research to focus more on its cancer therapies. In a letter to shareholders, the company stated that it will no longer use the stock symbol "HIV" since "we have 'matured' into a cancer product development company." Cel-Sci, which is listed on the American Stock Exchange, will now use "CVM" as its stock symbol (not to be confused with "CMV" or cytomegalovirus). The change in focus, according to the letter, is "a result of the compelling responses the Company is seeing with its cancer product, Multikine™, in Phase II human clinical studies. Additional human studies with the HGP-30 AIDS vaccine, even though the results look promising and the vaccine is urgently needed, will need to be funded through outside resources."

PMC Now Aventis Pasteur

Pasteur Mérieux Connaught (PMC), the French vaccine manufacturer, has changed its name to Aventis Pasteur. The change reflects the merger of Rhône-Poulenc Rhorer, PMC's parent company, and Hoechst, the German pharmaceutical giant. ◆

EU Funds South African Vaccine Education and Advocacy Efforts

by Michelle Rotchford Galloway

On 20 January 2000, the European Union (EU) officially committed R11 million (about US$1.7 million) to a four-year project aimed at community advocacy and education around HIV vaccine development in South Africa. The project, called HIVAC (HIV Vaccine Action Campaign), will be carried out by a consortium including the South African Medical Research Council, the National AIDS Convention of South Africa (NACOSA), the Centre for the Study of AIDS at the University of Pretoria and the AIDS Legal Network, with additional players expected to join later on.

The EU award, funded from the budget for HIV/AIDS operations in developing countries, represents its first contract given directly to a science council in South Africa. The South African AIDS Vaccine Initiative has also provided funds, with R820,000 granted for the first year and further support to be decided based on the project's progress.

The HIVAC project, which began in January 2000, will address the public health, human rights, ethical and legal issues involved in vaccine preparation. Its specific aims are:

- To meet a growing demand for education and information from communities and individuals (particularly those at the highest risk for HIV infection) on HIV vaccine research and development, so they can make informed decisions regarding potential participation in vaccine trials and eventual vaccination;
- To facilitate full community participation in the process of HIV vaccine development and utilization;
- To ensure protection of human and legal rights of potential HIV/AIDS vaccine trial participants, their immediate communities and the wider society;
- To foster and sustain political support for HIV/AIDS vaccines and other preventive interventions; and
- To support the development of systems for information flow and interaction among active players, one that also encourages the sharing of information and experience with other African countries and contributes to the global knowledge base. ◆

Michelle Rochford Galloway is based in Cape Town and is the managing editor of AIDS Bulletin, *a periodical published by the Medical Research Council of South Africa.*

Netherlands Second Government Contributor to IAVI

AIDS Fonds becomes partner of IAVI, organizes community vaccine meeting at European conference

by David Gold

On 7 December 1999, the Dutch government announced a grant of 5 million guilders (US$2.3 million) to IAVI for the year 2000, making it the organization's second government funder after the United Kingdom. At the same time, AIDS Fonds agreed to became IAVI's partner organization in the country.

"The Dutch Government expects that IAVI will play a leading role in vaccine development," said Hans Moerkerk, speaking on behalf of Eveline Herfkens, the country's Minister of Developmental Collaboration. Moerkerk said that the Ministry plans continued support of IAVI. "And we welcome the collaboration between AIDS Fonds and IAVI," he added.

Peter van Rooijen, director of AIDS Fonds, said, "the Netherlands is ready for IAVI. The grant from Minister Herfkens means that there is public support. The collaboration between AIDS Fonds and IAVI will work to strengthen support for AIDS vaccine development in Europe."

Established in 1985, AIDS Fonds' mission is to contribute to the global fight against HIV/AIDS through fund-raising, funding and education. Funding activities of AIDS Fonds are focused on scientific research, direct individual support, care, prevention, education and projects in developing countries.

"This commitment," said Seth Berkley, president of IAVI, "is an important milestone in the effort to accelerate the development of globally accessible AIDS vaccines. Noting that the Netherlands has a long history of collaboration with developing countries and has played an important leadership role in global HIV prevention efforts, Berkley said, "We salute the Dutch government's vision in furthering their commitment to HIV prevention, by helping to fund the development of AIDS vaccines."

Berkley also noted that the partnership with AIDS Fonds, IAVI's second partnership in Europe, is particularly important given the Netherlands' long history of collaboration with developing countries and its leadership in global HIV prevention efforts.

AIDS Fonds is playing an increasingly active role in pushing for accelerated HIV vaccine development. The foundation organized a meeting on community involvement in vaccine development at the 3rd European Conference on the Methods and Results of Social and Behavioral Research on AIDS. Held on 15 February in Amsterdam, the satellite session was chaired by UNAIDS vaccine chief Jose Esparza and included vaccine advocates from the Netherlands, the U.S. and Brazil. ◆

HIV Immunity and "Resistant" Sex Workers: An Interview with Sarah Rowland-Jones

Sarah Rowland-Jones is an immunologist at Oxford University's Institute of Molecular Medicine and a physician specializing in infectious diseases. In the early 1980s, Rowland-Jones began treating the first AIDS patients in London. That led her to work with Andrew McMichael, a leading researcher in cellular immunity at Oxford, where she leads a team on HIV immunity. Their findings, along with those of collaborators at Oxford and the University of Nairobi, form the basis of a vaccine being developed as part of an IAVI-funded vaccine development partnership.

IAVI Report: Can you tell us about your work in Kenya and how it got started?

Rowland-Jones: Our group works on cellular immunity to HIV, and in particular whether it can stop or control virus replication. We originally looked at infected people, but then became interested in whether the same responses can protect people who are exposed to HIV but have not become infected.

The first hints that this might be the case came from studies we did eight or nine years ago, in a baby born to a couple where the husband is a hemophiliac and his wife had become infected in the course of trying to have a baby. For most of its first year of life, it was unclear whether the child was infected or not, because there were still maternal antibodies present and the PCR test [for HIV DNA] wasn't reliable back then.

When the baby reached about nine months, we detected a very powerful CTL response, and we presumed this meant that it would turn out to be infected. But shortly afterwards, the CTLs disappeared, the baby was fine, and it became completely negative for antibodies. When we went back later with a better assay to look at those early time points, the virus counts were all negative. This was the first hint that you could make a T-cell response to HIV without actually being infected.

But in a baby born to an infected mother and then not exposed again, this could simply be an immunological memory, rather than a protective immune response. So we decided to look at people exposed to HIV over a period of time but who had not become infected, because that approach was more likely to make a link with genuine protection.

How did you go about this?

We did some studies in a group of sex workers in The Gambia, where about a third of the prostitutes are infected. Some of these women also turned out to have CTL responses to HIV.

And then we made contact with Frank Plummer and his group in Kenya. They had just described a setting where people with probably the highest level of HIV exposure documented anywhere in the world were staying uninfected. Frank felt strongly that this was probably due to some type of immunity, because they couldn't link it with any epidemiological factors. But they did find an association with certain HLA types [the "tissue" type, determined by genes which influence immune responses], which suggested an immune-mediated mechanism.

So we teamed up and started the Kenyan studies to look at whether the resistance of those women was related to an immune response to HIV.

A few of the women who stopped sex work have become infected. Can you give us an update?

The number of women who fall into what we call the "resistant" category is close to a hundred, at the moment. The operating definition of resistance is women who have definitely been exposed but have remained HIV seronegative for three years or more. So it's a fluid number, between ten and twenty percent of the whole cohort.

For many, many years, there had been no seroconversions in this group. But some of these women are now older, and looking for activities other than prostitution. Others had a longish break, or cut down the number of partners they were seeing. In the last couple of years, a total of 10 women who were previously categorized as resistant have become infected.

How do you explain these infections after so long?

At this point we know that at least three of the women had the sort of CTL response we documented previously, which raises the question of how effective these responses really were. But we don't have blood samples taken immediately before they became infected, so we can't say what their immune responses to HIV were at the actual time of infection. That raises a big question about what is really happening. We do know that they weren't infected by "escape mutants," or viruses with mutations in the regions that the immune responses were previously directed against.

The correlation appears to be with giving up prostitution altogether, or reducing the number of clients. So the conclusion at the moment is that the immunity to HIV in these women is relative rather than absolute, and that you need continuing exposure to the virus to maintain it.

The best parallel is the relative immunity that some people build up to malaria – that is, people who spent many years in malaria-endemic regions without getting sick and then move somewhere without malaria. When these people return home, they often get malaria, while previously it seemed that they were immune. It appears that the immunity isn't absolute, but requires repeated exposure to keep it at a high enough level to afford protection.

What do the infections in these women mean in terms of prospects for a vaccine?

I don't think it's necessarily bad news. Of course, it is very sad for the women. They believed that they were immune to HIV, and so did the team working with them. They were being seen by television crews every few weeks, so they knew something was special about them. They all had different theories about what it was, but there was definitely a feeling they were protected in some way.

Scientifically, it means that their resistance isn't due to an absolute block in infection. That's good news – it's not that they can't be infected because of some non-immune mechanism we haven't thought about. We looked quite closely

at this a few years ago, to see whether there was something else – for example, an HIV co-infection, or some other block to their cells become infected. We didn't find anything. But we couldn't eliminate the possibility that another mechanism having nothing to do with immunity was stopping HIV.

But the fact that some women became infected when their exposure decreased makes it more likely that they were protected by an immune mechanism. That implies that you can achieve immune-mediated protection against HIV infection, but you need to do it better than a regular, daily exposure to HIV, which is not a very good way of avoiding infection.

What else do you know about the womens' immune responses?

Rupert Kaul, who is part of the Oxford group and has been doing a lot of this work in Nairobi, has looked closely at women who took a break from sex work but didn't become infected, and then resumed sex work. During the time they're not exposed he can see the CTL responses detected by ELISPOT assays dipping down and sometimes disappearing altogether. Then, when the women are exposed again, their responses come back. So it really is consistent with exposure being necessary to maintain the responses. What we can't explain is why some people get infected when their responses disappear, while others get challenged again and start to boost their responses.

We will be studying all of this in much more detail. What we now know is that the infected women's immune responses look like those of other infected people. But there are hints that they are responding to different viral antigens than they did when they were uninfected. There are also hints that, for a particular HLA type, the responses to one epitope might be more common in people who are exposed and uninfected, whereas people who are HIV-infected respond to a different epitope through the same HLA molecule. That's very intriguing, and we will do a lot more experiments on this. For vaccine development, we've got to look quite hard at which responses made by exposed but uninfected people are unique to them.

For vaccine development, we've got to look quite hard at which responses made by exposed but uninfected people are unique to them.

We're trying to build up a picture of what those might be; to define these new CTL epitopes that you only get responses to in people who appear to be protected, or at least in the exposed, uninfected category.

Have you looked at viral setpoint in these women?

This is an important point. We certainly want to find out whether their viral setpoints are different from those in women who didn't have immune responses to HIV before becoming infected. But most of these infections are relatively recent, so it's a bit early to know if the setpoint has been reached. We're collecting plasma, and we will look at the kinetics of the viral load for a year or eighteen months after infection.

It's known that African populations show much more genetic diversity, including HLA diversity, than any other peoples. How might this impact vaccine development?

This is a very important issue. We've spent a lot of time building up profiles of the HLA types of the women in the cohort, so we now know a lot about HLA diversity within that group. There are some molecules that we are discovering for the first time in this population. For example, one of the Kenyan prostitutes in the resistant category had three new HLA molecules, which we sequenced. It turned out that they had never been reported before. I think this issue is going to be important for many populations.

But other things are also relevant to the susceptibility and outcome of HIV infection in Africans, and we've been trying to look at those in terms of chemokine receptors and other polymorphisms. It is important to realize that these populations are quite distinct in those factors.

Does this mean that, apart from differences among HIV strains, different populations might respond differently to the same vaccine?

I think it is feasible to make vaccines that will work for a lot of people in different populations. Where the diversity will probably matter most is in terms of measuring the immune response. I think it is worth putting in the time and effort to characterize the HLA types in population you're working in. So even if the vaccine works equally well in different populations, what you measure might be quite different for the HLA types in Africa and in Europe. And if the vaccine approach works, it would be not too difficult to adapt it to include information about HLA types and responses in different populations.

But we don't know for sure, since HIV is the first case where researchers have looked hard at genetic differences between populations while trying to characterize immune responses in great detail.

What has it been like on a personal level to work with these women?

When you're working with this kind of group, it's not the numbers but the individuals who are important. I think it's very significant that we are learning so much from a group that is not very highly regarded by society, something we wouldn't be able to learn from other people or in other settings. These women are making a big contribution to vaccine development.

The other very important people are the clinicians in Nairobi. They are a very dedicated and amazing group that has provided care and support, and helped the women to support one another, for fifteen years now. That's one of the most valuable things about the whole project, over and above the research.

Are the women advised to use condoms?

Yes. The use of condoms in the group as a whole has definitely increased with a lot of input and help from the team. So there's been a dramatic fall in other sexually acquired infections over the years, and a difference in the general health of the women. But the HIV exposure rate is still very high – about 10% per year, according to Frank Plummer's most recent data. But that's fallen from a peak of about 25% a few years ago. So, it's still pretty intense HIV exposure.

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Viewpoint

Live Attenuated AIDS Vaccines: Let's Keep the Research Moving Forward

by Mark A. Wainberg

Within the next decade, HIV will probably become the world's leading cause of death. At this time, over 35 million people are known to be infected by the virus. In developing countries, where most of these people reside, the vast majority of them cannot afford anti-retroviral drugs. There is, accordingly, a growing consensus that the development of a safe, effective vaccine against HIV represents the world's most urgent public health priority.

Unfortunately, it is taking much longer to develop such a vaccine than most scientists anticipated back in 1983-84, when research on HIV began in earnest. There are many reasons for this. One is the tremendous degree of antigenic variability seen among different clinical isolates and subtypes of HIV. Another is the particular routes of transmission used by HIV, which will probably require that a vaccine elicit both mucosal and systemic immunity.

Against this background, however, a number of different HIV vaccine design concepts have been articulated. One of the most important is the classical approach of using attenuated virus strains (i.e., live but greatly weakened) that have only a limited capacity to replicate but can stimulate specific anti-HIV cellular and humoral immune responses. Attenuated vaccines have been widely used around the world to protect against other viral diseases, including smallpox, polio, yellow fever, measles, and mumps. In each case, the immune response evoked by these poorly-replicating vaccine strains is able to clear the attenuated virus and to provide long-lasting protection against re-infection by the same pathogen. However, there are no attenuated vaccines in use against diseases caused by retroviruses, the group of viruses that includes HIV and others able to integrate their genome into host cell chromosomes.

The present safety problems should not lead to complete pessimism or an abandonment of research on live attenuated AIDS vaccines.

And therein lies a major problem: How can we ever be sure that an attenuated form of HIV, integrated into the host genome, is safe over the long term? This concern is highlighted by findings that vaccination of newborn macaques with attenuated strains of SIV (simian immunodeficiency virus) can cause fatal immune system disease (1,2), No one should try to downplay either this problem or the fact that an attenuated HIV vaccine strain might be spread by vaccinees to their sexual partners, and by vaccinated women to their babies.

A key aspect of safety is to find ways of preventing attenuated HIV vaccine strains from reverting to virulent forms. The issue arises for attenuated HIV and SIV strains because these have been weakened not by irreversible chemical or physical treatments (as for other attenuated vaccines) but by the presence of potentially reversible genetic changes in the viral genome. Indeed, genetic reversion is exactly what seems to have happened with the above-mentioned attenuated SIV vaccine, which was made from virus deleted in all or part of the *nef* gene (an important determinant of pathogenesis in wild-type viruses. Similar findings come from cohorts of people infected with *nef*-deficient HIV strains. Originally, these individuals appeared to be long-term non-progressors, but many have now developed serious HIV disease, although this usually occurred at least 10-15 years after infection (3-4).

Although the mechanisms by which these *nef*-deleted strains recover virulence are not fully known, other studies suggest that the high degree of complexity in HIV and SIV genomes allows new mutations to arise that can compensate the original (attenuating) ones, thereby restoring viral pathogenesis. For example, our group has sought to attenuate HIV by introducing deletions (approximately 16-20 nucleotides) into the region between the viral LTR and the *gag* gene. This region of the viral genome does not encode any protein but plays a role in regulating HIV replication, since it encompasses the dimerization initiation site (DIS) involved in forming a crucial replication product (the viral genomic double-stranded RNA). We found that deletion of major segments within DIS initially slowed HIV replication in tissue culture, but over time the virus gradually re-established a high level of replication. Why? Remarkably, it turned out that point mutations occurred in four different gag proteins (MA, p2, NC, and MA), and that all four changes were essential for full restoration of replicative capacity (5-6).

Fortunately, a potential way around this problem is suggested by studies in our lab showing that larger deletions (50-60 nucleotides) in the non-coding region of SIV provide significant long-term attenuation, with no reversions observed over 6-24 months in tissue culture. We now need to see whether these viruses will pass the safety test following injection into newborn macaques and, ultimately, whether they are capable of protecting animals against challenge with virulent SIV.

We must also try to limit the likelihood of reversion in other ways. One approach may be to include in these *nef*-deleted strains (or in other attenuated variants) mutations in genes that may render the virus less capable of reversion, for example, the M184V mutation in reverse transcriptase (RT). This methionine valine substitution is responsible for HIV resistance to the anti-

viral drug 3TC, but also marginally attenuates viral fitness (7). Recombinant RT molecules containing the M184V mutation also have a decreased mutation rate compared to wild-type enzyme (8).

Natural history studies are slowly laying to rest another major safety concern. Several researchers have argued that integration of HIV might promote the occurrence of leukemias and lymphomas by turning on latent cellular oncogenes near the integration site. Thus far, the evidence suggests that non-immunosuppressed, long-term survivors of HIV do not have detectably increased rates of these or any other cancers.

So where does this leave us? It would be foolish to argue that the development of a live, attenuated HIV vaccine is not fraught with biological and ethical problems. On the other hand, would it be ethical to stop or delay research into such a product if other, safer approaches fail and we then have a world with 100 million HIV-infected people instead of the 35-40 million we now have?

The safety problems with live attenuated HIV vaccines to date should not lead to complete pessimism over the prospects for this approach, or to abandonment of research. The need for a safe, effective vaccine against HIV is simply too urgent to overlook any potentially promising approach. While we all hope that current strategies based on recombinant gp120, viral vectors such as canarypox, adenovirus and other vectors, or naked DNA will be successful, the reality is that we must have fallback positions if they fail.

It will be at least 5-10 years until the world is ready to attempt Phase I vaccination studies with a live attenuated form of HIV. But let's continue basic research in this important area and be ready with a product that will have at least passed safety studies in animals, in the event that the approaches now rightly receiving top priority fail to yield an effective vaccine.

Mark Wainberg is director of the AIDS Centre at McGill University in Montreal and president of the International AIDS Society. His lab initially identified 3TC as an anti-viral drug (together with BioChem Pharma Inc.) in 1989 and has remained active in drug discovery and HIV prevention-related research.

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INTERVIEW WITH SARAH ROWLAND-JONES
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Can you update us on the Oxford/University of Nairobi team's progress with their vaccine?
Things are moving through the various regulatory bodies. We hope to start Phase I trials of both the DNA and MVA constructs in Oxford sometime between June and August. Then, as soon as we have reasonable indications of safety, we will move into the Kenyan Phase I trial. If all goes well, that should happen by the end of this year.

Have the infections in the "resistant" Kenyan women changed your strategy in any way?
If it turns out that some immune responses are more protective than others, we will have to look at changing the vaccine construct in the future, to incorporate that information. So it's an important area of study. But we haven't been claiming to have a perfect vaccine. It was based on the best knowledge we had at the time, but which may change in the future.

IgA has also been associated with some level of protection in these women. What are your thoughts on the possible role of IgA?
I'm not an expert in IgA. But some people who work in this area have doubts about the way those assays were done. So it's controversial. We recently reported, and Rupert Kaul also found, that the CTL levels in the mucosal cervix are relatively enriched in the women who are resistant, compared to those who are HIV-positive. We think it's quite important that there are HIV-reactive cells in the mucosa, presumably at the site of challenge. That's another area we need to think more about – generating that kind of mucosal immunity.

How has the general population in Kenya reacted to the proposed HIV vaccine trials? Has there been much press coverage about it?
There's been pretty steady press. The vaccine initiative was launched last January and initially got very good press. Then there was a sort of backlash of people saying that it was experimenting in African populations. There was worry that people would become HIV-infected through the vaccine trial. It was dealt with very well by the Kenyan team. Overall, there's a lot of enthusiasm for the trial, and a lot of good publicity, although one of the major churches has said that vaccine trials shouldn't be encouraged because if people thought they were protected through a vaccine, it would encourage promiscuity.

What do you do about that?
It's not something you can reason with.

What population will the participants come from?
The idea at the moment is to draw from people working in the university – probably not a student population, but people working in the medical school who are reasonably educated and can most easily understand the protocol of the trial.

Is there any access to anti-retroviral therapies in Kenya?
Only for a very small handful of people. The drugs are increasingly being provided for pregnant women in a short course of an affordable regime. For other adults infected with HIV, it's very rare, except for a small group of people who can

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group at the ADARC and Progenics Pharmaceuticals, Inc., a New York-based biotechnology company (recently published in *Journal of Virology*, January 2000). In intact virions, the envelope protein is a trimer of three gp120 molecules weakly associated with three molecules of gp41. But the complex is very unstable, and once dissociated, its individual components tend to be poor at eliciting neutralizing antibody (although they often induce high levels of non-neutralizing antibodies). Moore's approach was therefore to genetically modify gp120 so it is joined with gp140 via a stable disulfide bond, resulting in a correctly folded trimer that closely resembles the native structure. Their next step is to test whether this oligomer can in fact generate neutralizing antibodies in animals (see also "Industry Insider", page 8).

Delivering HIV Antigens to Dendritic Cells

Several speakers presented studies on targeting HIV antigens to dendritic cells, a key antigen-presenting cell, as a way to enhance immune responses. Drew Weissman of the University of Pennsylvania described his lab's novel system for accomplishing this very simply by loading HIV-RNA (rather than DNA, as in most other methods) into peripheral blood dendritic cells. Using a reporter gene to calibrate the system, they achieved an astonishingly high transfection (uptake) rate of over 90% (compared to 1-2% for DNA transfection), although such high efficiencies were not obtained in other cell types, such as T-cells or macrophages. The transfected cells also expressed the foreign RNA with high efficiency (despite the lack of cap or polyA structures required for DNA expression), producing 1000-fold more protein than transfected B cells or macrophages. Transfection with HIV *gag* RNA led to potent activation of anti-*gag* CD8+ killer T-cells and CD4+ helper cells *in vitro*. Weissman's group is now attempting to bypass the in vitro step and deliver RNA directly to dendritic cells *in vivo*, which could help pave the way to an RNA vaccine.

Other investigators followed the movements of transfected dendritic cells that were re-injected into animals. Ralf Ignatius of Rockefeller University presented studies with rhesus monkeys showing that the cells retain their ability to migrate to lymph nodes and generate T-cell responses. He also found that immature and mature dendritic cells infected with an SIV-canarypox vector induced SIV-specific T-cell responses in animals, with the latter cell type being more potent.

Jason Gardner of Chiron described the development of a Sindbis virus vector that can deliver *gag*-DNA into immature (but not mature) dendritic cells at efficiencies of 30-50%, leading to transient antigen expression. By using fluorescently-labeled vector particles, they showed that transfected cells injected intradermally into mice migrated to the draining lymph nodes and triggered robust CD8+ T-cell responses in mice.

Other Viral and Bacterial Vectors

In the poster sessions, information on a number of different viral and bacterial vectors was presented. Researchers from ADARC reported a salmonella vector expressing SIV *env* that, in lab tests, could be selectively delivered to antigen-presenting cells; they plan to test the constructs in rhesus macaques. Stanford University researchers presented data showing that Salmonella bacterial vectors could deliver antigen by oral administration in mice.

Judy Leiberman of Boston Center for Blood Research also presented data on an anthrax toxin vaccine expressing HIV *env* and *gag*. In tests in mice, the vaccine generated a measurable CD8+ T-cell response. The construct also generated measurable CTLs in lab tests using human blood cells. These findings, according to the researchers, "lay the foundation to advance this approach to clinical testing."

Researchers from Japan's National Institute of Infectious Diseases reported data on a Sendai virus vector. The researchers immunized two cynomolgous monkeys intranasally with a Sendai vector expressing SIV *gag* at 0, 4 and 14 weeks. After challenge with SIV mac239 at week 22, the two monkeys show "significantly lower levels of SIV" compared with two control monkeys.

Genetic Differences Effect Immune Responses to Canarypox Vectors

Individuals with different genetic backgrounds appear to have significantly different responses to candidate HIV vaccines, according to a study by researchers at Aventis Pasteur, the University of Alabama at Birmingham and Duke University. Earlier studies have shown that a number of different genetic characteristics correlate with slow HIV progression (HLA alleles B27 and B57), rapid progression (B8 and B35), and neutral progression (other B alleles).

Another study showed that individuals with genetic characteristics associated with slower HIV progression seem to have greater CTL responses to HIV-canarypox vaccines.

After taking blood samples from four different trials of ALVAC canarypox vectors, the researchers found that vaccinated individuals with the two HLA types associated with slower progression showed greater *gag* and *env*-specific CTL responses. But interestingly, those with HLA types associated with rapid progression did not show lower CTL response than individuals with HLA types associated with neutral progression. However, vaccinees with the B8 allelle did show a slight trend toward lower CTL responses to the vaccine.

Correlates of HIV Transmission

What factors determine whether an HIV-infected person will transmit virus heterosexually? Tom Quinn of Johns Hopkins University presented results from a study of this question in 415 discordant couples in Rakai, Uganda. The strongest predictor of transmission proved to be viral load: the researchers saw no transmission from HIV-infected people with viral loads below 1500 copies/ml, while the likelihood of transmission rose 2.45-fold with each 10-fold increase in viral load up to 50,000. These results are highly relevant to vaccine strategies, since they suggest that vaccines which "blunt" viral

load without preventing infection might still significantly reduce transmission. Aside from viral load, age also correlated with transmission, with older people transmitting less frequently. Putting the two correlates together, this meant that young couples with high viral loads are most at risk (35 transmissions in 100 discordant couples per year). Circumcised males were less easily infected and slightly less likely to transmit, while rates of male-to-female and female-to-male transmission were not significantly different within a given level of viral load.

Attitudes and Risk Behavior in the HAART Era

Researchers from the U.S. Centers for Disease Control and Prevention presented results from a survey of HIV-negative people in high-risk U.S. populations on risk behavior practices and level of concern about becoming infected. The survey included approximately 300 high-risk individuals: one-third men who have sex with men (MSM); one-third injection drug users (IDUs); and one-third high risk heterosexuals from STD clinics. Overall, 31% said they were less concerned about infection (range was 25-41%, with the lower figure from MSM and higher one from IDUs), while 17% reported being less careful in their HIV-related risk behaviors (range of 13-25%, highest among Hispanics and African-Americans). Among MSM, less concern about infection correlated with riskier behavior.

The researchers also found that willingness to participate in HIV vaccine trials was similar in all three groups. The most widely-cited reasons for participation were perceived self-benefits and helping to stop the spread of AIDS. Most commonly cited concerns were the potential for side effects from the vaccine, fears of contracting HIV from the vaccine and social stigmatization from participation. Participants expressed a desire for support with any vaccine-related complications, for future availability of the vaccine to their community, and for trustworthy and accurate information on the trial and product to be tested.

Preparing for HIV Vaccine Trials in Brazil

A team of researchers led by Mario Schector of the Federal University of Rio de Janeiro presented data with implications for conducting HIV vaccine trials in Brazil. The researchers tested blood samples from 1050 individuals attending an HIV testing site in Rio de Janeiro. Using sensitive assays, they found evidence of recent infection with HIV in 84 samples. Using these numbers, the researchers estimated HIV seroincidence in this population to be 1.9 per 100 person-years among heterosexual women and 2.8 among heterosexual males. In addition, 55% of those surveyed said they would definitely participate in a placebo-controlled HIV vaccine study.

Schector's team also presented data on HIV incidence and the use of post-exposure prophylaxis (PEP) among MSM in Rio de Janeiro. In their cohort, there was a sero-incidence of 3.2 per 100 person years. A total of 202 subjects were recruited and given education on PEP. Of these, 62% reported receptive anal intercourse in the previous six months and PEP was used 36 times. In what could have a significant impact on HIV vaccine trials in Brazil, the researchers conclude that the demand for PEP within this type of cohort was substantial.

Gary Nabel on NIH Vaccine Center

Gary Nabel, Director of the NIH's Vaccine Research Center, gave an update on the work of the Center, which is expected to open by September 2000. Nabel is planning to bring together at least 10 to 12 senior scientists and noted that Norman Letvin and Gordon Douglas, former president of Merck Vaccines, are now working with the Center on a part-time basis, as part of what he described as "The Dream Team". The VRC Director noted that progress in AIDS vaccine research will accelerate efforts to develop vaccines for other diseases. "We are making progress," he said, "and this is the time to redouble our efforts." ◆

Online Conference on Economics of AIDS Vaccines

The International AIDS Economics Network (IAEN) will host an online conference examining economic issues in AIDS vaccine development and deployment, to run from mid-April until the end of May. IAVI and the World Bank's AIDS Vaccines Task Force are sponsoring the event.

The six week conference will be moderated by Stefano Bertozzi, a physician and health economist who is director of health economics for the National Institute of Public Health in Mexico and a professor at the Centre for Economic Research and Education. He formerly worked at UNAIDS, where he was coordinator for the Department of Policy, Strategy and Research.

The conference will focus on issues related to the demand and supply of HIV vaccines. Background readings will be available on the IAEN website prior to the start of the conference. Once it begins, participants will be able to share their views on these issues and respond to one another, with the moderator providing comments and posting summaries along the way. The aim is to stimulate a lively exchange of views that will spur progress towards resolving some of the unknowns on the economics of AIDS vaccines.

Registration information and a preliminary collection of background materials are available at the IAEN website: www.iaen.org/vaccine. ◆

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Aventis Pasteur and a US$1 billion donation from SmithKline Beecham to eliminate elephantiasis.

Raymond V. Gilmartin, chairman, president and CEO of Merck & Co., said that "given recent scientific advances in understanding the biology and immunology of HIV infection," Merck has increased its efforts to develop an AIDS vaccine. "Our objective is to develop a vaccine that would be effective against multiple strains of the virus, thereby increasing the vaccine's global utility," Gilmartin said. Merck recently began a Phase I trial of an HIV-DNA vaccine.

Aventis Pharma's CEO, Richard Markham, called upon world leaders to begin addressing the "enormous ethical, political, economic and social issues" surrounding AIDS vaccine development. "We must deal with these hard issues now or else we could wind up with a scientific achievement and a public failure – an AIDS vaccine that people will be afraid to take, be unable to pay for or be available only to a privileged few," Markham said. Aventis Pasteur is developing a number of different candidate HIV vaccines, including the canarypox-based vectors.

> *If we don't address the hard issues now, we could wind up with an AIDS vaccine available to only a privileged few.*
>
> – Richard Markham, CEO, Aventis Pharma

IAVI, which was represented at the summit by its president, Seth Berkley, was praised by President Clinton as "a model public private partnership" for its role in accelerating the development of affordable AIDS vaccines. Berkley announced at the meeting that IAVI intends to triple, to six, the number of new AIDS vaccine candidates it will sponsor this year.

Other corporate leaders at the summit included Donald Francis, president of VaxGen, Sean Lance, chairman and CEO of Chiron, Jean-Pierre Garnier, CEO of SmithKline Beecham, and John Stafford, president and CEO of American Home Products Inc. Foundation officials at the summit included William Gates Sr., co-president of the Bill and Melinda Gates Foundation, Gordon Conway, president of the Rockefeller Foundation, Timothy Wirth, president of the United Nations Foundation and Herbert Brown, president of Rotary International.

The assembled leaders expressed broad support for President Clinton's Millennium Vaccine Initiative, a comprehensive plan to increase global usage of existing vaccines and create new incentives for the development of new vaccines against the world's major infectious killers ñ AIDS, tuberculosis, and malaria.

The Millennium Vaccine Initiative includes the following elements:

- A US$50 million contribution to the vaccine purchase fund of the Global Alliance for Vaccines and Immunization;
- U.S. support for the World Bank to increase low-interest loans for health services by as much as US$900 million annually;
- Significant increases in federally-funded basic research on diseases that affect developing countries;
- A US$1 billion tax credit on sales to developing countries of vaccines against malaria, TB and AIDS; and
- A call to G-7 partners to ensure a future market for these vaccines.

SmithKline Beecham's Garnier, for example, commented: "The President's Millennium Vaccine Initiative – to provide tax credits to companies for sales of eligible vaccines – will now provide industry with an important new incentive to launch research and development efforts into tropical disease areas," a field which he said "has always been challenging because of the complexity of the scientific research and difficult local economic conditions."

Don Francis of VaxGen, which is now running two Phase III trials of an HIV vaccine, said: "The majority of HIV infections occur in less developed countries, many of which will need financial assistance to purchase vaccines. The Administration's Initiative, and multimillion-dollar contributions from private foundations and the World Bank – all of which were discussed at the meeting – would make tremendous contributions toward helping these countries acquire life-saving vaccines sooner and in larger quantities."

"President Clinton has put forward a balanced and forward-looking plan that should energize vaccine development at every level, from the university lab bench to the pharmaceutical industry board room," IAVI's Berkley said.

Clinton's plan for tax credits appears to be gaining support. In a 14 March editorial, *The New York Times* noted that, "With any luck, the benefits for mankind (from the vaccine tax credits) could be spectacular."

Separately, legislation was introduced in the Congress that would both codify the President's initiative and enact other measures aimed at spurring vaccine development. The bill, known as the Vaccines for the New Millennium Act of 2000, was introduced by Senators John Kerry (D-Mass.) and Bill Frist (R-Tenn.) and Representative. Nancy Pelosi (D-Calif.).

In addition to incorporating the President's initiative, the measure would provide a tax credit for industry research and development expenses for AIDS, malaria and TB vaccines, authorize a US$10 million government contribution to IAVI, and create a Lifesaving Vaccine Purchase Fund administered by the Treasury Secretary. It also authorizes an advance appropriation of US$100 million a year over ten years, to the Lifesaving Vaccine Purchase Fund, to be used for the purchase and distribution of vaccines for malaria, tuberculosis, HIV, or any infectious disease which kills more than one million people.

The legislation was endorsed by the AIDS Vaccine Advocacy Coalition, VaxGen, the Gates Foundation and IAVI. ◆

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obviously the most controversial, given theoretical safety concerns of anti-host toxicities, so it has received the least attention. But some antibodies generated by this strategy seem quite potent, so the strategy must be considered further. It's clear from recent passive immunization studies that the right type and level of neutralizing antibody can protect against HIV, so this is an obvious priority.

What are the biggest challenges in initiating AIDS vaccine trials in developing countries?
There are a number of concerns. They include fears about testing vaccines without studying them first in industrialized countries; scientific issues relating to the candidate vaccine; and assurances about access if the vaccine is effective.

It's going to be a long process, so we have to cut through the myths associated with developing an AIDS vaccine, including testing these vaccines in the developing world.

To simply make a vaccine on the outside and bring it into a country is just asking for trouble. You need real partnerships from day one.

How do you do that?
I know, from working in industry that the best way is to build trust through real partnerships. So we want to initiate partnerships on day one of the development program. It's also important that all agree on accelerated development timelines from the beginning and get up-front agreement from regulatory authorities on the critical path to Phase I trials. With this approach, we believe we can move into clinical trials 18-24 months after starting the partnerships.

To simply make a vaccine on the outside and bring it into a developing country for clinical trials without having built up that level of good will is just asking for trouble. And some companies now face issues they didn't anticipate, because they haven't built up good will.

Is it feasible to imagine developing country partners producing the vaccine?
Some countries, such as India, China, and Brazil, have long track records of producing vaccines. So it's feasible and doable. Weíre trying to establish technology transfer as part of our partnerships, where manufacturing capabilities exist.

IAVI has conducted a series of scientific think-tanks. What's the goal?
To stay abreast of the field and identify issues where we can make a difference. Initially, we were just looking at identifying the best approaches. Now, we're also beginning to identify some impediments to product development.

For example, one challenge with alphavirus vectors is large-scale production. So IAVI brought all the players together, which is unique because we had competing companies around the table. But the issues are so complex that everyone agreed to discuss them as candidly as possible. And the result is that IAVI will explore production of certifiable cell lines for alpha virus vaccines.

Another example is our think-tank on live-attenuated vaccines. We are reviewing strategies for learning more from the live-attenuated model, information that could help in prioritizing vaccine approaches.

Where do you see IAVI's program in two years?
We should have innovative products – most likely improvements over first-generation candidates – entering human trials. At the same time, we will have begun head-to-head testing in humans and animals, to prioritize which vaccines to move into efficacy trials.

Do HIV clades matter in vaccine development?
It makes sense to try to match the vaccine as closely as possible with the viruses circulating in the country where you're doing trials. But it's unrealistic to think that we'll have regional HIV vaccines. Ultimately, we need Phase III trials comparing a matched and unmatched vaccine, because we can argue about clades until the end of the day; but only a trial will answer the question.

What is most frustrating in trying to move products forward?
Key obstacles include intellectual property issues and the unwillingness of many companies to look towards a greater goal by working together. We'd like to test the best candidates and prioritize them in head-to-head studies. But sometimes you don't have the rights to a promising vaccine, or a company might say, "it's not in our interest to test our product with yours." This is not an unreasonable position for a company, but it can impede the global effort. Nobody yet has developed creative strategies to overcome this.

And the urgency issue is given lip service but is still not taken seriously by some in industry or government. That's where IAVI comes in. With its small size and catalytic role,. IAVI has the potential to make a difference. By driving innovative products into trials, we can serve as a vaccine biotechnology incubator, and eventually hand off promising candidate vaccines to large pharma to complete development and licensure.

And the urgency issue needs to be raised again and again, focusing on the developing world. Ten years ago, Jim Curran (former official at the U.S. Centers for Disease Control and Prevention) said: "HIV is winning the war." And today, it's far worse than anyone would have imagined.

One of IAVI's strategies has been to use intellectual property rights generated from its research to ensure increased access to a vaccine. I would imagine these negotiations were not always easy.
We call our strategy "social venture capital" and yes, the negotiations can be challenging. But every deal is different. Sometimes, we're working with academic investigators who've never made a vaccine, other times, with small start-up companies that view their intellectual property, rightly so, as their crown jewels. And larger companies are sometimes just not interested, or set requirements beyond IAVI's resources. But we've already closed three deals for new vaccine approaches, and one more will be announced soon. So,

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afford private medicine – for them, the full range of therapies is available. But it really is a tiny minority.

What is the incidence of HIV in the general population in Kenya?
In the antenatal clinic, which is probably the best sort of indication, it's about 15-16% percent in Nairobi. But it's much higher in the western parts of Kenya; almost twice as high.

Is there concern about whether people will have access to this vaccine if it is effective?
That's a very major question. People want as much access to it as possible. Now.

How does a researcher answer this?
It's quite difficult, isn't it? First, we have to find out whether the vaccine works. But the length of time this takes can seem unreasonably long for people who want to have it, and that's very frustrating to people. It's hard to explain why it takes so long.

Some companies are talking about testing these vaccines in HIV-infected people on HAART. What are your thoughts on that?
It seems like a very reasonable approach, because the studies we've done in HAART-treated people show that their CTL responses diminish – within a few months after starting treatment, it's below detection by some assays. So augmenting HAART with a vaccine or some other mechanism that induces HIV-specific CTLs seems like a good way to improving treatment efficacy. It may also allow us to use short-course treatments, which would be much more feasible for developing countries.

Are you optimistic about overall prospects for an AIDS vaccine?
Yes, I am. If there was no natural immunity to HIV, I would be pessimistic. But I think the studies in these resistant people imply that, even if it's rare, there really is natural immunity to HIV. It may not be perfect, and it may not be easy to generate. But if it at least exists, then it is feasible to do the same thing, if not better, with a vaccine. If we hadn't found natural immunity in anybody, then I would have a much gloomier outlook.

Do you think it will be possible to develop a vaccine that targets a cellular immune response without boosting people periodically throughout their lives?
I don't know. We don't know enough about CTL-inducing vaccines. It's still a very novel concept.

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obviously we're able to find common ground.

As IAVI's resources grow, people will ask about milestones for judging whether its programs are moving forward. What are your milestones?
Initially, our key milestone will be moving products into Phase I trials, especially in developing countries. We'll then identify the better products, based on these trials. I agree with those who say we don't want to set arbitrary milestones of getting a specific number of vaccines into clinical trials, because you want to make sure they're the best vaccines.

But you have to start somewhere. So, I have no qualms about setting milestone plans, in the public arena, for IAVI's R&D program, and trying to meet them.

Will an AIDS vaccine make money?
Yes. It may not be a mega-market immediately, but eventually the market will be enormous. And I'd love to be in a position of discussing how to improve market share for a licensed HIV vaccine.

How would you get an AIDS vaccine out to the world once it's developed?
Access issues are going to be complicated. Eventually, an AIDS vaccine will be a pediatric vaccine. But in the beginning, you're going to have to target adolescents and high-risk adults, and historically, these groups have been difficult to reach. So IAVI and others must consider how to get vaccines to those populations and who will pay the costs.

I think IAVI should go a step further and do a demonstration project with an already-licensed vaccine. We could target these groups in a particular region, so we can collect data on what works, by the time an AIDS vaccine is available.

Is it possible to develop an AIDS vaccine by 2007?
We have to keep that as a goal. But realistically, the only way we'll get there by 2007 is if one of the vaccines currently in clinical trials is found to be effective. Data from VaxGen's gp120 efficacy trial should be available in a couple of years, and if NIH decides to do a canarypox-gp120 prime-boost efficacy trial, data might be available by 2004. But we need to plan both for success or failure, and to continue driving other candidates forward as fast as possible.

Some in the scientific community have been skeptical of moving sub-optimum vaccine candidates into Phase III efficacy studies. Why do you think that is?
A lot of reasons. You can't do an unlimited number of Phase III trials. And, frankly, in AIDS, a negative trial might have a more damaging effect than we might imagine. But with that said, we have to go forward. If people think we can rely on three monkeys and thirty human volunteers to get answers, they are mistaken.

So somebody has to go first. And, just as importantly, somebody has to go next. In that way, VaxGen has added a lot.

In the same way we first demonstrated the feasibility of doing clinical trials in developing countries a few years ago, VaxGen's demonstration that an AIDS vaccine efficacy trial can

Letter to the Editor

To the Editor,

I feel compelled to point out that the work with herpes simplex virus recombinants (HSV) described in the *IAVI Report* ("Report from Cent Gardes," November-December 1999) is a collaborative effort between my laboratory and the laboratory of David Knipe of Harvard University. Knipe's lab made the HSV recombinants and demonstrated expression of SIV proteins. My lab did the monkey experiments, antibody measurements and virological measurements. Paul Johnson's lab did the CTL measurements.

Also, 3 of 7 immunized animals showed protective effects against challenge with pathogenic virus (cloned 239), in contrast to the 5 of 7 against nonpathogenic virus stated in your report. I hope that this clarifies the data and our respective roles in case the study. We continue to be excited about the prospects for the next round of experiments with improved HSV recombinants.

Overall, I enjoyed this issue of the *IAVI Report* very much, as always, and I look forward very much to reading it every two months. I think "An interview with..." is particularly unique and something that you can be proud of.

Ronald Desrosiers
Director, New England Primate Center
Southborough, Massachusetts, USA

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be conducted in the developing world will accelerate the movement of other candidate vaccines into Phase III trials.

Should a vaccine that provides partial protection get licensed? And how do you define protection?

These are hard questions. And again, that's why we need long-term efficacy trials. There is no way around that. We won't know the validity of surrogate markers until we've some efficacy trials. I think if a vaccine is 50-60% effective and safe, it should be licensable. But regulatory agencies need to provide guidance to manufacturers on the targeted level of efficacy to shoot for. This is critically important in designing trials.

Regarding protection, the closer we get to sterilizing immunity, obviously the better off we will be. Whether AIDS vaccines can modify a person's immune responses to control or eliminate HIV infection is still not known.

If IAVI can help answer this question and move ahead a number of different approaches that get us closer to an effective vaccine, we will have made a significant difference.

IAVI Moves Headquarters

IAVI has moved its international headquarters to 110 William Street, 27th floor, New York, NY 10038-3901 USA; phone: 1-212-847-1111; fax 1-212-847-1112; e-mail: iavireport@iavi.org; website: www.iavi.org.

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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Lean in structure and catalytic in nature, IAVI focuses on three key areas: accelerating scientific progress; education and advocacy and creating a more supportive environment for industrial involvement in HIV vaccine development.

IAVI is a UNAIDS Collaborating Centre. Its supporters include the Rockefeller, Alfred P. Sloan, Starr, William H. Gates, Until There's A Cure and Vincent P. Belotstky, Jr. Foundations, as well as the U.K. and Dutch Governments, the World Bank, UNAIDS, the National AIDS Trust and Fondation Marcel Mérieux. IAVI also receives support from Crusaid, the Elton John AIDS Foundation, Levi Strauss International, Angel Music, Ltd., Glaxo Wellcome and generous individuals around the world.

VACCINE BRIEFS

Reports Highlight Epidemic in Key Countries

Three new reports highlight the impact of AIDS on countries with particularly severe HIV epidemics: South Africa, India and Nigeria. A report by ING Barings, a Dutch finance company, described the devastating impact AIDS is having on South Africa. According to the report, within the next five years, the epidemic is expected to significantly slow South Africa's economic growth. By 2005, it is expected that 27% of all mine workers and 22% of all transport workers in the country will die from AIDS.

A report by the chair of India's Economic Planning Commission warned that the number of HIV infections in the country could reach 10 million by 2010 and that the "government alone does not have enough resources to tackle the problem." UNAIDS estimates that 3.5 million people in India are currently infected with HIV.

And according to a report by Nigeria's Health Ministry, that country is also on the edge of an AIDS explosion, with national HIV prevalence rates now at 5.4%, up from 1.8% in 1991. The report noted that in some parts of the country, as many as 21% of all adults are HIV-infected. The worst affected area is the north-central part of the country.

Canadian Vaccine Network Funded

In February, the Canadian government announced that it will fund the Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Diseases (CANVAC) as one of three new Centres of Excellence. CANVAC is a network of Canadian researchers in immunology, virology and molecular biology working to develop vaccines for cancer and viral infections including HIV and HCV. The network will receive C$4.75 million per year for the next four years. AIDS researcher Mark Wainberg of McGill University in Montreal hailed the grant as "a major commitment of the Canadian government in support of HIV vaccines. Development of an HIV vaccine constitutes the world's most important public health goal, and this announcement could not have come at a more opportune time."

Upcoming Vaccine Meetings

The French Agence Nationale de Recherches sur le Sida (ANRS) is sponsoring a meeting on HIV/AIDS vaccine development on 5-7 May, 2000 at the Institut Pasteur in Paris. The meeting is likely to attract key AIDS vaccine researchers from Europe and the North America. NIH and UNAIDS are co-sponsoring the meeting. For more information, call 33-(0) 1-56-81-15-00, or fax 33-(0)1-43-25-26-26.

The First International Conference on AIDS Vaccine Development and Immunotherapy will be held on 28 June-1 July in Palm Beach, Florida. Several well-known researchers are part of the meeting's organizing committee, including Ron Desrosiers, Andrew McMichael, Marc Girard and Malcolm Martin. Further information is available at: www.intmedpress.com/vaccine.

The 3rd Annual Conference on Vaccine Research will be held in on 30 April-2 May in Washington, DC. This international meeting will focus on the full range of vaccine-related issues and is sponsored by the National Foundation for Infectious Diseases. Co-sponsors include NIAID, CDC, FDA, the Sabin Vaccine Institute and the World Health Organization. For more information, see the conference's website at: www. nfid.org/conferences.

Steve Wakefield Joins VTN

NIAID's HIV Vaccine Trials Network (VTN) has appointed Steve Wakefield its Director of Community Education. Wakefield, a respected vaccine advocate, has served as executive director of two Chicago-based NGOs, Test Positive Aware and the Northern Lights Ministry. He has also served as chair of AVAC's Board of Directors and HIVNET's community advisory board. Wakefield will be based in Seattle at the Fred Hutchinson Cancer Research Center.

Rose McCullough Gets Top AVAC Post

Rose McCullough has been appointed executive director of the AIDS Vaccine Advocacy Coalition. A microbiologist by training, McCullough joined the organization in 1999 as its first Policy Director. She has worked in public policy advocacy for organizations such as the Sierra Club, League of Women Voters, and the American Association of Retired Persons. AVAC also announced that Allison Bauer, an attorney, will succeed McCullough as policy director.

New Additions and a Departure at IAVI

A number of key positions have been filled at IAVI. Claudia Schmidt has been appointed clinical trials consultant in the R&D Program. Claudia's most recent work was in Uganda (through an appointment at Case Western Reserve), where she helped coordinate the NIH-sponsored Phase I canarypox trial. Donna Murphy, formerly of Save the Children, is now working in the Development Department as vice-president for major gifts and donor strategy. Sandi Glass, who previously worked at the Albert Einstein College of Medicine in New York, is the administrative director of IAVI's R&D Department and Sheenagh Day is now working in IAVI's European Office. Sheenagh's background is in family planning, reproductive health and genetic counseling.

We also note that Suman Raghunathan is leaving IAVI to take a position at the New York Immigration Coalition. Suman has worked at IAVI for the past two years, most recently as editorial and production assistant for the *IAVI Report*. We will miss Suman's dedication, exceptional spirit and commitment and wish her well in her new position.