

IAVI REPORT

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UNAIDS to Publish Guidelines on Ethics of Vaccine Trials

by Patricia Kahn

A UNAIDS "guidance document" on the ethical conduct of HIV vaccine trials should be ready for publication by the end of May, 1999, according to Jose Esparza, the agency's HIV vaccine team leader. The document's release comes after a two-year process that surveyed the views of people with a stake in the trials, both in industrialized and developing countries, and wrestled with some bitter controversies.

The original UNAIDS goal was to produce a consensus statement on ethical standards, emphasizing the issues that arise when vaccines produced in the

industrialized world are tested in developing countries. Opinions were canvassed through a series of meetings, including three regional workshops held in Brazil, Thailand and Uganda in April, 1998, that brought together diverse constituencies (AIDS researchers and physicians, ethicists, human rights lawyers, public health and policy officials, journalists and representatives of NGOs and affected communities).

Workshop participants discussed the setup of a hypothetical AIDS vaccine trial, talking through such issues as the challenges in obtaining truly informed consent and how

to ensure that participating communities receive a fair share of the eventual benefits of the research.

Each workshop reached consensus on the major issues, and in most cases the three regions also agreed with one another. But they were deeply divided on one key point: whether anti-HIV triple-drug therapy must be provided to participants who become infected during vaccine trials even if the drugs are not generally available in the host country – a controversy that has since enveloped the UNAIDS process and the entire ethics debate. Current guidelines for

continued on page 3

INSIDE THIS ISSUE

UNAIDS to Publish Ethics Guidelines

-1-

Gates Gives IAVI US\$25 Million

-1-

Vaccine Briefs

-2-

Bangkok Conference Highlights Global Vaccine Issues

-5-

Vaccines Still A Side Issue at Retrovirus Conference

-6-

Keystone Holds Meeting on HIV Vaccines

-7-

World Bank, EC Look to Boost AIDS Vaccine Development

-9-

AIDS Vaccines and Biotech Companies: An Interview with Therion's Dennis Panicali

-11-

India Launches AIDS Vaccine Program

-15-

Gates Gives IAVI US\$25 Million to Expand Scientific Program

With new Sloan gift, US\$50 million raised towards overall US\$350-500 million goal

With a US\$25 million grant from The William H. Gates Foundation, IAVI will significantly expand its scientific efforts to develop a safe and effective AIDS vaccine. The gift is the largest charitable contribution in the history of the AIDS pandemic, and comes on top of an initial US\$1.5 million commitment to IAVI at the World AIDS Conference in Geneva last June.

"Melinda and I want our children – and all children – to grow up in a world without AIDS," said Bill Gates, the founder of the Gates Foundation and chairman of Microsoft Corp. "A widely-distributed vaccine can help make the goal of a world without AIDS a reality.

Shortening the time it will take to find a vaccine can save millions of lives. We're proud to be supporting the heroic work of IAVI in this gift." "Bill and Melinda Gates' historic act of generosity will allow us to significantly accelerate the scientific effort," said IAVI president Seth Berkley. "With 16,000 new HIV infections a day, 95% of them in developing countries where there is little access to treatment, we have no time to spare." At the same time, the Alfred P. Sloan Foundation made a new grant of US\$2 million to IAVI, bringing the Foundation's total commitment to US\$5 million.

Wayne Koff, IAVI's vice president for research

continued on page 14

VACCINE BRIEFS

Planning Session for NIH Vaccine Center

The newly-appointed head of the NIH's Vaccine Research Center (VRC), Gary Nabel, held a two-day strategic planning session on 16-17 April 1999 at the NIH campus in Bethesda. About 35 people attended the meeting, including researchers from within and outside NIH as well as a number of activists. Leading NIH officials, including Harold Varmus and Anthony Fauci, also attended. Groundbreaking ceremonies for the Vaccine Center's new building are reportedly being planned. Among the expected attendees are U.S. President Bill Clinton. The building will be named for former U.S. Senator Dale Bumpers and his wife Betty, a vocal advocate for infant immunization. Nabel's appointment as VRC head, first reported in the *IAVI Report*, was announced in March.

Peter Young Appointed AlphaVax CEO

Glaxo Wellcome's vice president for HIV therapeutics, Peter Young, has been appointed president of AlphaVax Vaccines. The North Carolina-based company was formed to develop VEE replicon technology into commercial vaccines. In 1998, IAVI announced that it would invest US\$4.6 million in a collaboration between U.S. and South African researchers to help move AlphaVax's HIV-VEE replicon vaccine into human studies. That same year, Wyeth Lederle Vaccines agreed to use the AlphaVax technology to develop vaccines for a wide array of diseases. IAVI's Seth Berkley hailed the selection, calling Young "a respected and visionary industry leader, who will help the company develop its candidate HIV vaccines as quickly as possible."

Shiu-Lok Hu Joins IAVI China Effort; Wienold Working in Germany

Shiu-Lok Hu, a researcher at the University of Washington, has agreed to assist IAVI in exploring the development of HIV vaccine research programs in China. "We are excited that Shiu-Lok will be helping IAVI in this important area," said IAVI's vice president for research and development, Wayne Koff. Hu was one of the first investigators to test a prime boost AIDS vaccine combination (vaccinia plus gp160). IAVI will also be working with Matthias Wienold, a German physician and AIDS activist, in exploring opportunities to expand German efforts in AIDS vaccines.

New IAVI Staff

Nicholas N. Gouede and Kay Marshall have recently joined IAVI as communication specialists. Gouede, a native of the Ivory Coast, will be overseeing IAVI's communications and advocacy efforts in developing countries. His most recent work was with the Population Council. Marshall, a native of Arkansas, will coordinate the production of IAVI's information materials. She previously served as public relations manager for the National Down Syndrome Society.

AVAC Publishes HIV Vaccine Trial Handbook

The AIDS Vaccine Advocacy Coalition (AVAC) has published a book on HIV vaccine trials, *HIV Vaccine Handbook: Community Perspectives on Participating in Research, Advocacy, and Progress*. Compiled and edited by Bill Snow, the book is a useful resource for people involved in any aspect of AIDS vaccine trials. Snow, an indefatigable vaccine advocate, is a co-founder of the Washington, DC-based group. He also serves on the NIH's AIDS Vaccine Research Advisory Committee. To order the book, contact AVAC at: www.avac.org.

Uganda Canarypox Trial Starts

Uganda's first AIDS vaccine trial was officially launched in February. The vaccine being studied, a canarypox vector (ALVAC vCP205), is manufactured by Pasteur-Mérieux-Connaught. The purpose of the trial, which is sponsored by the U.S. NIAID, is to evaluate immune responses

among those vaccinated. It is being conducted at two Uganda locations - the Joint Clinical Research Centre (JCRC) and the Virus Research Institute. A total of 40 volunteers will be enrolled. The lead Ugandan researcher is Roy Mugerwa of Makerere University. Also overseeing the trial is Peter Mugenyi, director of the JCRC. Preparations for the trial began in 1992 after Uganda was identified by the World Health Organization as one of the countries with a capacity to participate in HIV vaccine trials. Mugenyi reports that preliminary results from the current trials may be available after six or seven months. The vCP205 vaccine has already been tested with no significant side effects in more than 800 volunteers in the U.S. and France.

VaxGen Begins Phase III gp120 Trial in Thailand

A Phase III trial of VaxGen's bivalent gp120 vaccine began in Thailand in March. Researchers expect to enroll 2,500 former intravenous drug users from 17 drug treatment centers in Bangkok in the 30-month trial. The vaccine consists of pieces of the HIV envelope gp120 from two different HIV strains, one of them a clade E Thai-based primary isolate. According to Jose Esparza of UNAIDS, the trial "provides a good lesson on how vaccine trials can be conducted in an open, united manner." VaxGen also reported that it has now enrolled more than 2500 of its goal of 5000 participants in the U.S. Phase III gp120 study.

New NIAID AIDS Vaccine Programs

NIAID announced the creation of two new AIDS vaccine programs. The Vaccine Production Contracts will provide funds to produce pilot lots of HIV candidate vaccines, while the HIV Vaccine Design and Development Teams program will be available to groups of researchers with development experience. To be eligible for the development team awards, potential awardees must have identified a promising vaccine concept and envisioned a product worthy of targeted development. The "team" program will fund 1 to 5 teams at a total of up to US\$10 million per year. For more information, contact the NIAID AIDS vaccine website at: www.niaid.nih.gov/daids/vaccine.

Australians to Test DNA/Fowlpox Combination

Human studies of a combination HIV DNA/fowlpox vaccine could begin sometime this year in Australia. A workshop conducted by the country's National Council on AIDS and Related Diseases on 25-26 March concluded that the combination was ready for further development. A Phase I safety and immunogenicity trial in HIV-infected individuals is planned, with about 40 people expected to be enrolled. The Australian researchers would like to move into larger trials in a number of Asian countries, including Vietnam or Cambodia. IAVI president Seth Berkley attended the meeting, which was held in Sydney, to discuss possible areas of collaboration.

South African Initiative Launched

In an attempt to accelerate AIDS vaccine development efforts, South Africa recently launched its own AIDS vaccine initiative. The South African AIDS Vaccine Initiative (SAAVI), as it has been named, will be led by Walter Prozesky, former head of the country's Medical Research Council (MRC). Key partners in the initiative include the South African government and Eskom, the country's national power company. SAAVI has the full support of the MRC's president, William Makgoba (who is also a member of IAVI's Board of Directors.) In its early stage of development, the initiative expects to raise approximately R50 million (US\$8 million). SAAVI's recent solicitation of proposals for AIDS vaccine-related grants has, according to sources, received a strong response from researchers.

clinical trials – the World Medical Association's (WMA) "Declaration of Helsinki" and those of the Council for International Organizations of Medical Science (CIOMS), which extend the Helsinki agreements to international settings – set the "best proven" treatment standard, albeit with some ambiguities and contradictions.

The dilemma for HIV vaccine trials arises because triple-drug therapies have barely penetrated most countries where the AIDS epidemic is at its worst – yet vaccines can be most easily and cheaply tested in these high-incidence regions, since it takes far fewer trial participants to see a vaccine's effect when the infection rate is high. Another contributing factor is that trials may need to monitor not only whether the candidate vaccine blocks infection (which few vaccines do), but also an alternative: that infection occurs as usual but the vaccine mitigates its effects by preventing virus from taking hold, delaying the onset of disease or reducing its severity and/or transmission (the way many vaccines probably work). Yet the latter possibility could be difficult to detect in people on anti-retroviral therapy, depending on when the therapy is initiated. Scientists are now considering one potential solution: whether measurements of "viral load" (HIV levels in the blood) shortly after infection but prior to starting treatment might be a reliable indicator of whether a vaccine affects disease progression (see *IAVI Report*, April-June 1998).

The three regions each had a clear view. Asia and Africa, home to most of the world's hardest-hit countries – which have the biggest stake in getting an effective vaccine rapidly – accepted the "highest practically attainable" standard of care for trial volunteers, largely out of concern that requiring triple-drug therapy would create a huge barrier to mounting any trials. In contrast, participants at the Latin American workshop (led by representatives from Brazil, where triple-drug therapy is widely available, but including several representatives from countries where it is not), along with the U.S.-based advocacy group, Public Citizen, argued that trials must provide triple-drug therapy, according to existing ethical guidelines (and ideally continue them for the person's lifetime). The outcome was a stark illustration that, with few exceptions, "a country with 20% of the people infected sees things very differently than a country that perceives AIDS as a treatable problem," says Esparza.

With strong emotions on both sides, forging a consensus among the regions proved impossible. Heated debate at a meeting in Geneva two months after the workshops failed to resolve the treatment issue, leading UNAIDS to propose that the decision be left to the host and sponsoring countries of each trial (see *IAVI Report*, October-December 1998). To many, the compromise represented a practical solution that respected developing countries' own needs and priorities. But to a minority, it reflected an unethical lowering of standards for vulnerable populations and a concession to vaccine manufacturers, who would presumably be expected to foot much of the bill for the anti-retroviral drugs (see box, right, for a sample of opinions).

The impasse over treatment also led UNAIDS to switch strategies: with a consensus document no longer realistic, they decided to formulate the guidelines as a UNAIDS position statement, informed (but not bound) by the opinions voiced at the meetings and

workshops. "At this point we have to bite the bullet and say, 'this is what we believe,'" says Esparza. The document is now being written within the UNAIDS secretariat (by consultant Dale Guenter, the Canadian physician who served as rapporteur for the regional meetings and wrote their final reports) rather than externally (bioethicist Robert Levine of Yale University wrote the early drafts). The finished product will be released together with a complete record of the two-year process, including all meeting reports and submitted comments about earlier drafts (with their writers' consent).

Although its contents are not yet finalized, the document's general direction and recommendations are clear. An overall principle, says Esparza, is to move away from rules that take a "protectionist" attitude to developing countries and towards a model which empowers them to decide on their own behalf, within a framework of minimum standards. "Even very poor countries should have the right to negotiate in their own interest," he says. "But we must also be careful not to swing the pendulum too far the other

continued on page 4

Differing views on ethics and treatment standard

"Focusing only on relatively few people in a vaccine trial misses the point of the whole demand for access. This is dangerous and wrong. The treatment issue should focus on everyone."

— Luis Santiago, AIDS Vaccine Advocacy Coalition, U.S.

"We've spoken to several thousand people about vaccine trials and no one has ever raised the treatment issue. This comes from people who don't see the reality of going to funerals every week. . . . In ethics, one size does not fit all. A study in Malawi is not the same as a study in New York."

— Salim Karim, Centre for Epidemiological Research, South Africa

"If economics were not a problem, would anyone be against providing treatment? . . . Researchers will naturally go to the cheapest places to do trials. . . . We must separate economics from ethics."

— Dirceu Greco, Federal University of Minas Gerais, Brazil

"As long as sponsors can identify a willing host country, researchers will have the guidance document to back them up in their withholding of known effective therapy, in direct defiance of CIOMS and the Declaration of Helsinki. . . . If all that has been decided is that the host country should decide, what has been accomplished?"

— Peter Lurie, Public Citizen, in a letter to Jose Esparza, January, 1999, U.S.

"Ethical principles are the same everywhere but risks and benefits vary, depending on rates of infection and availability of treatment. That is why decisions must be made locally. The most ethical thing to do is move the best science forward as fast as possible and make it available to countries that want access to it."

— Seth Berkley, IAVI

way so that two countries can do anything they agree on, since they are not negotiating as equals in terms of power and money. This is our challenge: to avoid paternalism without saying that anything goes."

Perhaps the most far-reaching recommendation in the guidance document (accepted by all three regions without much controversy) is that developing countries should have the right to conduct Phase I and II trials of a vaccine even if it has not been tested previously in the country where it was made. (Such trials are not considered ethical under current CIOMS guidelines.) While the original intent of this rule was to prevent "guinea pig" scenarios in which inferior or risky products are tested in impoverished people, the flip side, says Esparza, is that "this requirement can prevent development of products appropriate for developing countries, which is NOT ethical."

On the treatment issue, UNAIDS will endorse the basic compromise proposed in Geneva while emphasizing that trials should aim to provide the best proven therapy. "We want to encourage the highest standard as a goal," says Esparza. "But not reaching it shouldn't be a reason for not doing the research." While recognizing that this decision will be criticized by those who regard provision of triple-drug therapy as the only ethical way forward, Esparza points to the area of human rights, where incremental improvements, or "progressive realization," rather than immediate attainment of the ideal, is more widely accepted.

On other issues, the guidelines will generally reflect the consensus of the three regional workshops. All agreed that HIV vaccine trials must include a state-of-the-art prevention program, including behavioral counseling and access to condoms, sterile needles (where legal) and STD treatment, to minimize the chances that trial participants increase their risk behavior in the mistaken belief that they are protected from infection. Monitoring the quality of the prevention program, and ideally even providing it, should be independent of the trial's investigators.

Other key recommendations will focus on ensuring that participating communities share in the benefits once an effective vaccine is found. That assurance should begin by testing vaccines directed against HIV strains relevant to the host country (whether subtype as currently defined or some other definition of "immunotype," based on the latest scientific evidence) and extend to guaranteeing that high-risk communities in host countries have rapid and ready access to a successful vaccine, via mechanisms to be negotiated between the host and sponsoring countries before starting any Phase III trial. Yet some scenarios will be less than clear-cut, so the guidelines will stress the need to examine circumstances closely: for example, should a vaccine that is only 40% effective be made widely available? The answer may well be "yes" for countries

with a high HIV incidence, where such a vaccine would probably still be beneficial overall, but "no" for low-incidence countries, where possible increases in risk behavior after vaccination (resulting from vaccinees' sense that they are protected against HIV) may outweigh the benefits. The guidance document will also emphasize that making vaccines available is a shared responsibility belonging not only to the manufacturer but also to other parties, such as the governments of the countries involved and the relevant NGOs.

As UNAIDS finalizes its document, both the WMA and CIOMS are starting to consider revisions to their current guidelines for all types of clinical trials. The former, which compiled (and occasionally

updates) the Declaration of Helsinki, got off to a bad start with a draft revision that called for loosening informed consent rules, permitting use of placebos even where effective treatments exist (unless doing so would cause death or permanent disability) and for replacing the "best proven" treatment standard with the local standard of care in all clinical trials. The draft, which was not widely circulated for comment outside WMA member organizations, was heavily criticized even by moderates in the UNAIDS debate. "It effectively eliminates any obligation for researchers to provide

anything," said one. Last month, however, the WMA Council backed away from the draft and, according to WMA president Delon Human, will begin a new process involving broader consultation and a return to the existing guidelines as the starting point. "Our first objective will be protection of the patient," he told the *IAVI Report*. The CIOMS revision process has just gotten underway, and in particular will consider whether to follow the UNAIDS recommendation to revise their guidelines so that Phase I and II tests can be carried out in developing countries even for products that have not been tested in their country of origin.

For any ethics guidelines to work effectively in the developing world, potential host countries need local expertise to evaluate clinical trial proposals. Helping to build that capacity is now high on the agendas of UNAIDS and NIH's Fogarty International Center, both of which are sponsoring workshops and programs that bring people together to share ideas and practical experience on the ethical questions they will face as more HIV vaccines move through the pipeline into clinical trials. ♦

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people infected sees things
very differently than a country
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— Jose Esparza

Correction

In the last issue of the *IAVI Report* (January-March 1999), there were two errors on page 20. The chart "The Epidemic in Young People" should have read: "1.7 million young people in Africa are infected every year" and "700,000 in Asia and the Pacific are infected every year."

Bangkok Conference Highlights Global Vaccine Issues

by Wayne Koff

As efforts to develop an AIDS vaccine gain increasing attention, a growing number of scientific meetings are focusing on the topic. While the meetings vary in size and comprehensiveness, they can, at times, provide useful ways to measure progress in AIDS vaccine research and development.

The International Conference on HIV Vaccine Development: Global, Regional and Thailand Update was held on 15-19 March 1999 in Bangkok. Organized by Mahidol University, the Thai Ministry of Public Health and UNAIDS, the conference attracted an international cast of AIDS researchers and provided an opportunity for participants, particularly from Asian countries, to share information and perspectives on HIV vaccine development. Some of the highlights of the Bangkok meeting are summarized below.

Overview of Epidemic and Vaccine Development

Jose Esparza of UNAIDS reviewed the epidemic and recent advances in HIV vaccine development. More than 40 million people have now been infected with HIV and of these, 12 million have already died. Within Asia, India has 4 to 5 million HIV-infected people (*editor's note: see article on page 15 for the newest estimate*), China has approximately 400,000, and Thailand 780,000. HIV prevalence rates are greater than 1% of the population in Thailand, Cambodia and Myanmar, and nearly 1% in Indians 18-49 years old.

In terms of worldwide HIV variation, clade C accounts for approximately 48% of total infections (India, South Africa, etc.), clade A for 25% (central and western Africa), clade B, 16% (Europe, Americas, Japan); clade D, 4% (central/eastern Africa); clade E, 4% (Thailand and southeast Asia), and others 3%.

Esparza highlighted three new vaccine approaches: a Bacille Calmette-Guérin (BCG) HIV clade E vaccine being developed by Japanese researchers, and the two programs supported by IAVI, DNA plus MVA and Venezuelan Equine Encephalitis (VEE) replicons. He also discussed plans to merge the World Health Organization (WHO) and UNAIDS HIV vaccine programs, create ethical guidelines for AIDS vaccine trials (see page 1), and support advocacy and community participation efforts in developing countries.

New Recombinant Strains of HIV

Francine McCutchan of the Walter Reed Army Institute of Research (WRAIR) discussed the global diversity of HIV, including evolving classifications of types, groups, subtypes (clades) and intersubtype recombinants. HIV is divided into two types (1 and 2). HIV-1 is now classified into 3 groups: O,M,N. The new group N is based on a chimpanzee isolate and has only been found thus far in two individuals in Cameroon. Type O has been identified principally in Cameroon, Gabon, and Guinea. Group M is divided into subtypes A-J, with type E now considered a recombinant A/E strain and type I considered to be a

combination of A,G, and I. Other subtypes now identified as recombinants in certain regions: A/B is circulating only in intravenous drug users in Russia; D/F is circulating in central Africa; A/G in western and western/central Africa and B/C in Yunnan, China. In all more than 30 subtype recombinants have been identified. Regarding the global spread of HIV-1, South America has 80% subtype B, the remainder is F and C; Africa has all subtypes. HIV-2 is subclassified into subtypes A-E, of which A and B are only widely studied.

Targeting Dendritic Cells

Sarah Frankel of the U.S. Army's Henry Jackson Foundation discussed the role of dendritic cells in HIV infection and strategies to target these cells for vaccine development. Dendritic cells are considered to be the best antigen presenting cell in the body. Vaccine strategies for targeting these cells include: using unique routes of administration such as intradermal injections or Bioject gene guns; using vectors such as VEE that target dendritic cells; and administering stimulating cytokines to the skin before injection of the vaccine.

Ralph Steinman of Rockefeller University is studying a procedure where he removes dendritic cells from the body, inserts viral antigens into them and then reinfuses the cells back into the body. The strategy is being studied for flu and tetanus in nine volunteers. A single injection stimulates CD4 and CD8 responses. Frankel is planning to use the same methodology with canarypox for HIV.

U.S. Army Trials in Thailand

John McNeil of the WRAIR discussed plans to conduct a Phase III trial of three vaccine strategies in Thailand in 2002. The trial would compare an antibody-inducing vaccine, a cell-mediated immunity-inducing vaccine and a combination vaccine. Current plans are to compare DNA (Wyeth) plus gp120 to canarypox plus gp120. Due to the decreasing rates of new HIV infections in Thailand, the Army is looking at establishing new cohorts in other countries. These might include working with cohorts in Uganda and building a presence in Kenya.

NIH Programs

Rod Hoff of the U.S. National Institute of Allergy and Infectious Diseases (NIAID) reported on plans for Phase II/Phase III trial of a canarypox/gp120 combination. He noted, however, that only about 20 to 30 percent of volunteers in earlier canarypox prime boost studies show measurable CTLs at any single time point. Three different canarypox vectors are now being compared in a Phase I trial, with a [Phase II study set to begin later this year based on the outcome of the comparative trial](#). With this timetable, the Phase II/Phase III trial would not begin until late 2000, at the earliest. Hoff also reviewed NIAID's

AIDS Vaccines Still a Side Issue at Retrovirus Conference

By David Gold

The Conference on Retroviruses and Opportunistic Infections draws leading AIDS researchers, clinicians, journalists, industry officials and activists from around the globe. But vaccine research has largely been a side-issue at Retrovirus meetings and this year's conference, held on 29 January - 3 February 1999 in Chicago, was no exception. Nevertheless, there were some interesting vaccine-related reports.

Some Protection with Antibodies

A team led by WRAIR researcher John Mascola studied whether antibodies alone could protect monkeys against a pathogenic SHIV challenge. (SHIV is a combination virus with an HIV envelope and SIV core proteins.) The researchers passively transferred a combination of two human monoclonal antibodies and HIVIG (HIV immune globulin) to monkeys and then challenged them intravenously 24 hours later. Interestingly, 3 of 6 monkeys given the combination and 1 of 3 given only monoclonals were completely protected from infection (known as sterilizing immunity). The remaining immunized animals became SHIV-infected but had low viral loads and near-normal CD4 counts. Monkeys that received just HIVIG or one of the monoclonals became infected and had high viral loads, yet still had a more benign course of disease than the control animals, all 6 of which developed AIDS within 14 weeks.

Mascola also found that antibodies from the protected animals neutralized SHIV strains in lab tests. He concluded that a vaccine which induces true neutralizing antibodies should protect against HIV infection or disease, but that sterilizing immunity will probably only be achieved with very high levels of antibodies. The study does suggest, though, that lower antibody levels might offer partial protection against disease.

MVA and other Pox viruses

NIAID's Vanessa Hirsch reviewed poxvirus virus vectors and her ongoing research on MVA vaccines, in collaboration with fellow NIAID researcher Bernie Moss.

Overall, the four most widely studied poxvirus vectors are: MVA - a vaccinia virus passaged in chicken cells to make it attenuated; NYVAC - a genetically attenuated vaccinia virus; the ALVAC canarypox vaccines produced by Pasteur-Mérieux-Connaught, and "TROVAC" - a fowlpox virus.

In her study, Hirsch compared MVA constructs: 1) MVA encoding SIV *env*; 2) MVA encoding SIV *gag/pol*; 3) MVA-SIV *gag, pol, env*; and 4) a control arm. The monkeys were given four intramuscular immunizations and challenged at eight months with the pathogenic SIV E660. While all animals became infected with the challenge virus, the vaccinated monkeys had a significantly lower level of virus than the controls. Moreover, 2 of the 4 monkeys in the *env, gag, pol* group had normal CD4 levels. In comparison, two animals in the

control arm died very quickly with a rapid CD4 decline and all the other control animals developed AIDS within 6 weeks. All three MVA constructs generated SIV-specific CTL responses. None of the protected animals developed high levels of SIV antibodies, leading Hirsch to conclude that the protection correlates with cellular, but not antibody, response.

Adeno-virus associated Vector

Phil Johnson of the University of North Carolina at Chapel Hill presented data on a recombinant adenovirus-associated vector (AAV). The virus, which is part of the parvovirus family, has advantages: 1) it is non-pathogenic but generates a persistent expression of antigen; 2) it can accept a sizable insertion of viral genes; and 3) it is "hardy" virus - heat-resistant and easy to transport.

Johnson inserted SIVgp160 and *rev* into the AAV vector and immunized monkeys with the resulting construct. Nine months after a single immunization, the monkeys still showed measurable antibodies and CTLs.

These data, according to Johnson, suggest that "AAV can give, massive expression. The vector is not a virus anymore - it is like a DNA delivery system." So far, the only side-effects from the vector appear to be transient inflammation 3-4 days after immunization. AAV is also being tested as a vector in gene therapy for cystic fibrosis.

Mutant DNA

In a poster presentation, a team led by Larry Arthur at the NCI's Frederick Center reported on a candidate vaccine made by genetically altering SIV's nucleocapsid (NC) protein to create a non-infectious "mutant" SIV DNA. It is hoped that these particles with a defective NC will mimic a live attenuated vaccine. Arthur's team immunized monkeys with either the mutant SIV DNA or a control vaccine and then challenged them with pathogenic SIV. All control animals became infected and 3 of 4 developed AIDS within 56 weeks of the challenge. In contrast, 4 of 5 immunized monkeys were AIDS-free after two and a half years.

Comparing Different Envelopes

Researchers from the University of Rableais in Lyon, France compared five different Semliki Forest Virus (SFV) vectors. Like VEE and sindbis, SFV is an alphavirus. The SFV vectors used by the French researchers contained different combinations of HIV envelope antigens. The constructs encoded three envelope proteins from primary isolates of HIV and two from lab strains of HIV. According to the French researchers, the construct with a combination of all five envelopes inserted into the SFV vector generated the broadest immune responses in mice. ♦

Keystone Holds Meeting on HIV Vaccines

By David Gold

The year's most comprehensive conference on AIDS vaccines took place in Keystone, Colorado on 7-13 January 1999. The meeting, "HIV Vaccine Development: Opportunities and Challenges", was sponsored by the Keystone Symposium and attracted many of the world's top AIDS vaccine researchers.

Highlights of the meeting included:

Jack Nunberg's "Fusion Competent" Immunogen

Jack Nunberg of the University of Montana presented data on his "fusion competent" immunogen. Nunberg created the construct by mixing together monkey cells that carry the HIV envelope protein and human cells that carry the HIV receptor, CD4, and the CCR5 coreceptor. He then added formaldehyde to preserve the envelope protein "fused" to its receptors.

In CD4, CCR5 transgenic mice, Nunberg's immunogen generated antibodies that neutralize primary isolates of HIV from many different strains. In the same experiments, a gp120 vaccine (what he calls a "static immunogen"), was incapable of neutralizing these primary isolates.

Nunberg is collaborating with Therion Biologics, a Massachusetts-based biotechnology company (see interview, page 11), to develop a vaccinia vector expressing a fusion competent-like immunogen. In addition, the NIH is preparing to test the fusion-competent immunogen in monkeys. While Nunberg faces significant challenges in developing his construct into a candidate vaccine, the presentation of his findings was clearly one of the highlights of the meeting.

More Evidence that CTLs Protect

Norman Letvin of Harvard Medical Center/Beth Israel Hospital (and a member of IAVI's Scientific Advisory Committee) presented data strongly supporting the theory that CD8⁺ T-cells play a significant role in controlling SIV infection. Using a monoclonal antibody, Letvin's team was able to deplete CD8 cells in SIV-infected monkeys. When these CD8 cells were depleted prior to SIV infection, most of the monkeys failed to develop cellular or humoral immune responses and experienced a rapid disease progression. In comparison, only 2 of 6 monkeys with normal CD8 counts experienced rapid progression when infected with SIV. Similarly, when monkeys already infected with SIV were depleted of CD8 cells, rapid increases in SIV levels were seen. When the CD8 cells reappeared, SIV levels decreased significantly.

Herpes Virus Vectors

Ronald Desrosiers of Harvard Medical Center/New England Primate Center presented data on a number of herpes virus vectors his research team is evaluating. He began by noting the advantages of using herpes viruses as vectors: 1) they induce cellular and humoral immune responses; 2) these immune responses are persistent and durable; and 3) large amounts of genetic material can be inserted into the vector. One challenge in studying herpes simplex vectors (HSV) is that the virus grows poorly in rhesus monkeys.

Desrosiers compared a replication competent HSV vector encoding SIV *env*; a replication defective HSV vector with SIV *env* and a control vaccine in monkeys. The monkeys were challenged intrarectally with a homologous strain of SIV. Overall, 2 of 5 monkeys given the replication-competent HSV vaccine had no detectable challenge virus at any time; the other 3 had transient virus that later became undetectable. Of the two monkeys vaccinated with replication-defective HSV, one had no detectable virus. Notably, all three protected animals had SIV-specific CTLs.

Although the challenge virus was a homologous strain, it is difficult to protect against, according to Desrosiers. His team is now trying to optimize an HSV construct by including *gag/pol*. Desrosiers also noted that HHV-8 (the Kaposi's Sarcoma-associated virus) might also be an interesting vector. He concluded by joking that "in moving from live attenuated vaccines to herpes virus vectors, I'm going from the fire to the frying pan."

Promising MVA Data

Bernard Moss of NIAID discussed his lab's efforts, working with Vanessa Hirsch, to develop SIV MVA vaccines. Hirsch presented data at the Retrovirus Conference showing that the MVA constructs appear to lessen SIV disease progression in monkeys (see story, page 6).

Moss clearly believes that CTLs play a key role in providing the limited protection seen by the MVA constructs. He also reported that mucosal immunization of MVA may be one way to overcome pre-existing immunity to vaccinia due to smallpox vaccination. Moss immunized two monkeys with MVA-SIV, one of which had been given an earlier smallpox vaccine. The monkey that had not received the smallpox vaccine developed good SIV-specific CTLs; but the smallpox-vaccinated monkey developed no such responses. However, when this monkey was immunized intrarectally with MVA, measurable CTLs were generated, suggesting that mucosal immunization might overcome prior smallpox immunity. Looking to the future, Moss outlined plans to compare a number of new prime boost combinations in monkeys including: MVA/env protein; protein/MVA; MVA/MVA; DNA/MVA; and DNA/DNA.

Roundtable on HIV Vaccine Development

A roundtable discussion on AIDS vaccine development featured NIAID's Peggy Johnston, Emilio Emini of Merck, NIH Office of AIDS Research head Neal Nathanson and Bill Snow of the AIDS Vaccine Advocacy Coalition.

Johnston began with a brief overview of her plans and perspectives. She described the AIDS vaccine pipeline as a "pipette" and noted that "for a long time the research stagnated with an almost complete reliance on the private sector for bringing products into Phase I trials." Johnston outlined a range of NIAID programs designed to stimulate AIDS vaccine research. A critical goal of these

continued on page 8

efforts, she said, "is to widen this pipeline with quality candidates."

Emilio Emini, in his brief presentation, noted that Merck "wants to move as rapidly as possible into human studies." But, he cautioned, "it is absolutely essential that we have assays sufficient to measure what is going on. While (Norm) Letvin and others provided clear evidence that cellular immune response can inhibit HIV/SIV, we can't just settle on a single CTL measurement." Emini also presented data about one of the company's HIV DNA constructs. Monkeys were immunized with two different doses of the vaccine (encoding HIV *gag*) at 0,1,2,6 months. According to Emini, the DNA vaccine generated "good cellular responses in 7 of 9 animals at the highest dose."

When asked what they considered the most significant story of the conference, both Johnston and Emini pointed to Jack Nunberg's results and to emerging data on the importance of cellular immunity in containing HIV infection. In response to a question about whether liability concerns are limiting private sector investment, the Merck researcher said that, in his view, liability was a concern with everything industry does and was not unique to HIV vaccine development.

Chiron's Vaccine Program

Margaret Liu discussed a range of HIV vaccine approaches being pursued by Chiron, including: second generation DNA vaccines; alphavirus replicons; inserting DNA in alphavirus plasmids; and enhancing protein vaccines with new adjuvants.

With alphavirus vectors (which include sindbis, VEE and semliki forest virus), Liu stated, "you can make constructs that express large amounts of antigen." Chiron is developing sindbis replicons that generate "nice antibodies and CTLs" in mice. When asked about the safety of alphavirus replicons, Liu noted studies by AlphaVax's Bob Johnston suggesting that VEE replicon-infected cells appear to die,

"so the fear of integration should be minimal." She also noted that sindbis, unlike VEE, is non-pathogenic in its natural form. Chiron is also studying the use of DNA instead of viral particles in alphavirus replicons. The alphavirus vectors generate 3-100 fold increases in CTLs compared to regular DNA plasmids. Liu also described how new adjuvants can enhance vaccine immunogenicity. By using Chiron's M59 adjuvant with a hepatitis B vaccine, rates of seroconversion in humans jump to 60% after one dose (compared to 12% with the standard hepatitis B vaccine). She noted that other adjuvants being developed by Chiron seem to boost CTLs.

DNA Plus MVA Combination

Andrew McMichael of Oxford University discussed efforts of his lab, working with IAVI, to develop and test an HIV DNA/MVA vaccine combination. "The central question we are asking", said McMichael, "is whether T-cells, independent of antibodies, can protect against HIV." The Oxford researcher reported that very early data in monkeys vaccinated with SIV DNA and MVA containing a CTL epitope suggests that *gag*-specific CTLs were induced in 3 out of 3 monkeys. McMichael noted that while measurable CTLs are seen, additional boosts may be needed to maintain these responses, since they tend to fade. Asked whether he would consider using more of the *gag* gene, McMichael said "We will certainly consider it at some point." He noted that tetramer binding assays are becoming very powerful tools for examining immune responses to SIV/HIV vaccines.

McMichael praised IAVI's strategy of working with developing countries and obtaining access to intellectual property rights for developing countries. "We are developing, with IAVI, a clade A vaccine in Kenya. The reaction in that country has been very positive, because we are making a vaccine based on local strains."

The Role of Antibodies

Dennis Burton of Scripps Research Institute reviewed the possible role of antibodies in protecting against HIV. Research in animal models suggests that a very high and sustained level of antibodies would be required to prevent infection with HIV (sterilizing immunity). However, Burton suggested that "antibodies are still very much in the game even without sterilizing immunity." He also noted that antibodies might "buy time for a more effective CTL responses to develop." Burton said that future studies of antibody-inducing immunogens should utilize mucosal challenges that more accurately reflect most HIV infections.

"Self-Immunization" Therapy

In an interesting report, the Aaron Diamond AIDS Center's Doug Nixon described two patients who have controlled their HIV infection for a period of time, through what appears to be a type of self-immunization. Both patients were treated with a potent combination of anti-HIV drugs, but had been only intermittently adherent. When they were not adherent, their viral loads rose substantially. But once the patients went back on the drugs, HIV levels became undetectable again. Both patients again halted treatment and no rebound in viral levels has been seen so far. Nixon hypothesizes that the patients may have immunized themselves

Conference on Vaccines Held in Washington

The Second Annual Conference on Vaccine Research, held 28-30 March 1999, in Bethesda, Maryland, featured a number of reports on AIDS vaccine research. Researchers at the University of California at Los Angeles reported that heat inactivation of HIV appears to increase its antigenicity, possibly by exposing hidden epitopes. The finding, reported in the *IAVI Report* (Jan.-March 1999), provides more evidence that whole-inactivated HIV may hold promise as a vaccine. In another report, researchers from the University of California at Davis immunized monkeys with an SIV DNA vaccine (expressing *env*) and then boosted with either non-infectious proviral DNA or an SIV envelope protein. Interestingly, the animals boosted with the envelope protein showed increased viral loads and disease progression, compared to those given the proviral DNA boost. In addition, increased levels of antibodies correlated with higher levels of SIV. The vaccine meeting also featured the first Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences, which was given by NIAID's Peggy Johnston. ♦

World Bank, EC Meetings Explore Ways to Stimulate AIDS Vaccine Development

by Patricia Kahn

At a meeting on 13 April in Paris, major government donors to the World Bank strongly endorsed the Bank goal of developing financial mechanisms to accelerate AIDS vaccine development. The gathering of treasury and foreign affairs officials from a range of industrialized countries, along with representatives from four developing nations and from UNAIDS, IAVI and the European Union, met to consider if and how the Bank should use its unique position in financial and political circles to complement ongoing efforts by the health sector. In agreeing to support greater Bank commitment, the meeting's participants upheld the view expressed by Joseph Stiglitz, senior vice president for development economics and chief economist, who opened the meeting by pointing out that the AIDS epidemic is reversing the enormous gains in life expectancy and economic development achieved in many developing countries over the past three decades. Therefore, he told Bank sponsors, an AIDS vaccine for the developing world is a crucial component of the Bank's mission to reduce poverty and promote economic growth.

"This outcome is a strong statement of support," says IAVI president Seth Berkley, who was present at the meeting. "The Bank's donors could have said, 'this isn't our problem, we're a bank.' Their involvement gives a big boost to the effort."

The Bank's attention to AIDS as a development issue comes as the epidemic's ruinous long-range consequences in the developing world become increasingly clear. In the worst hit regions of sub-Saharan Africa, the lifetime risk of dying of AIDS is 40-50% and life expectancy is reduced by up to 30 years, according to Bank data and the U.S. Census Bureau (see chart, page 10). Many of the dying supported families, leaving their orphaned children to abandon school and earn money for other children and relatives – a devastating blow to their countries' futures. Another potential disaster-in-the-making was highlighted by a recent article in South Africa's *Sunday Times* (25 April 1999), which reported that 25% of randomly-screened students at one university were HIV-positive. Health care systems are also struggling to cope: costs are rising, treatments are often minimal at best and capacity to care for those with treatable illnesses is severely compromised.

The Paris meeting was convened by the Bank's AIDS Vaccine Task Force, a group formed one year ago with representation from all Bank sectors, plus IAVI's Berkley, to develop a set of options for its Board of Directors. So far, the Task Force has focused on three possible areas for action: increased policy dialog, aimed at raising the priority of AIDS vaccine development among governments and supporting whatever steps the Bank ultimately pursues; "push" mechanisms to increase support for vaccine research and development (R & D); and – the major area of emphasis – "pull" mechanisms to increase industry involvement, given that the private sector has so far invested little in AIDS vaccines.

Specific steps under consideration, according to Task Force co-chair Martha Ainsworth, include:

Expanding direct support for vaccine R & D. At present, the World Bank gives relatively little AIDS money through outright grants: US\$18 million to UNAIDS and its predecessor program at WHO over the period of 1986-1998, plus a total of US\$1.74 million in "seed money" to IAVI, beginning in 1996. Far more is given out through loans, mostly low-interest credits to the poorest countries – so far, the Bank has lent US\$765 million for dozens of AIDS-related projects, usually focused on prevention. "Push" mechanisms for accelerating HIV vaccine development are unlikely to involve substantially more grants, but could focus on expanding credits available to poor countries for development, manufacture and/or testing of vaccine candidates, especially for building infrastructure. Additionally, the Bank could use its weight to urge other funders to increase support for HIV vaccine R & D.

Further research into the potential market for HIV vaccines in developing countries. The Task Force's research so far shows that industry relies on market data from the industrialized world in making decisions on AIDS vaccines, while information about developing country markets is severely lacking. At the same time there is a perception among some companies that the latter market will be small and ability to pay uncertain at best. Concrete information is needed to fill this knowledge gap – for example, on how much potential buyers, especially governments and international agencies, would be willing to pay and under what circumstances. That, in turn, requires analyzing the many variables that will affect these decisions, such as a vaccine's price and ease of delivery (would there be a market for a vaccine that is 50%

effective? for one that requires three immunizations?).

Demonstrating to industry that demand for existing vaccines can be increased in developing countries. Industry concern that the developing world market for an HIV vaccine might be small is based partly on the fact that this has indeed

been the case for most new vaccines (e.g., hepatitis B, pneumococcus, rotavirus). Targeted efforts to turn this around could go a long way towards easing this concern, and pilot projects are now underway in several developing countries to expand loan programs for vaccine purchases.

Developing financial instruments to guarantee a good market for HIV vaccines in developing countries. Various options have been proposed, beginning with a "vaccine purchase fund" – a pool of money that the World Bank would commit for buying HIV vaccines when one becomes available. This could be done either by financing the fund now, so it can accrue interest over the coming years, or financing it

An AIDS vaccine is crucial for reducing poverty and promoting economic growth in the developing world.

continued on page 10

when a vaccine is much closer to licensure. However, some participants at the Paris meeting expressed reservations that the former option commits money so many years in advance rather than using it to save lives now (for example, by purchasing other vaccines). An alternative that "captured peoples' imaginations," says Ainsworth, is a contingency loan - a new mechanism of loan credits (at very low interest for the poorest countries) that would be agreed upon in the present but used in the future for purchase and delivery of an HIV vaccine.

The next step for the AIDS Vaccine Task Force is to turn its list of options into a concrete proposal for action, to be presented to the Bank's Board of Directors later this year. That will require further research, both internal and external, to evaluate the feasibility and the relative advantages and disadvantages of the different options. "We want to develop something that will really be used, and that industry will see as a strong signal," says Ainsworth.

While the World Bank works on identifying financial mechanisms for attracting more companies into the AIDS vaccine effort, the European Union (EU) is considering a complementary role that emphasizes regulatory and legal issues. That was the outcome of a two-day meeting ("Making an AIDS vaccine available in developing countries: An EC consultation," Brussels, 18-19 March 1999) organized by Lieve Fransen of the European Commission's Development Directorate (DGVIII) to collect technical advice on what role the EU should play. (The European Commission, or EC, is the EU's administrative body.) The gathering brought together diverse experts - specialists on public health, economic and legal issues plus representatives from developing countries, donor agencies, IAVI, the South African AIDS Vaccine Initiative (SAAVI), World Bank and UNAIDS - to discuss the key non-scientific barriers to making AIDS vaccines for the developing world and to identify those which the EU might fruitfully address.

The meeting covered a broad range of topics, including economic issues (market disincentives for industry and gaps in existing knowledge about markets) and various regulatory and legal obstacles. Given the EU's role as a policy-making body, the latter areas seemed to offer several

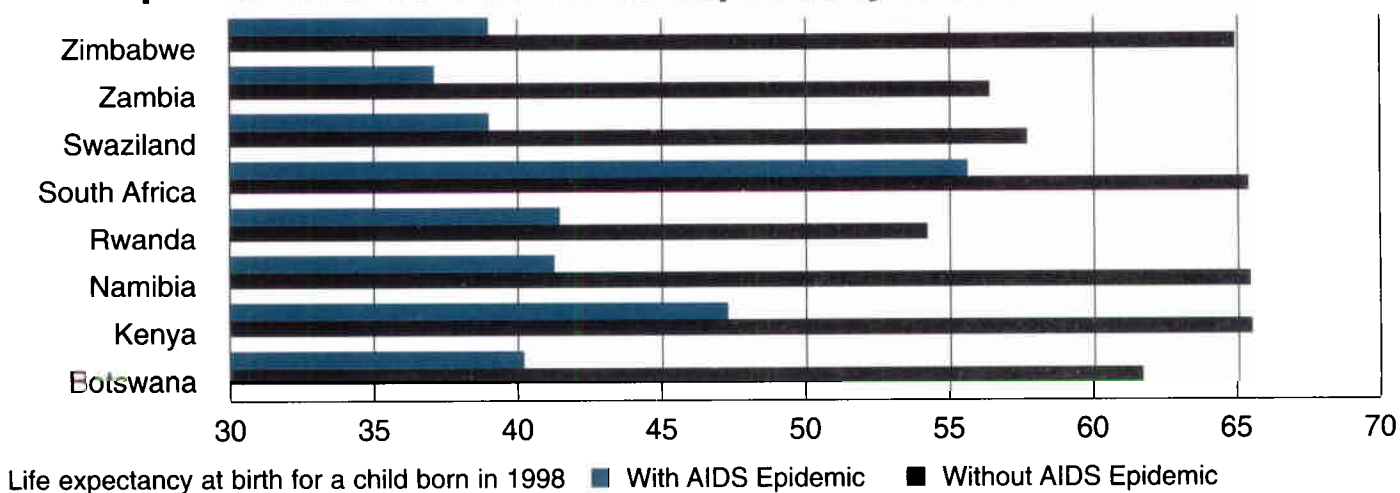
promising avenues for EU action.

One potentially useful strategy is already being pursued to encourage the development of "orphan drugs" (those which treat serious diseases but are unlikely to earn profits for the companies that develop them). A proposal to provide incentives for industry to invest in these products is now being finalized by the European Parliament, and includes measures such as 10-year exclusive marketing rights in EU countries, fast track mechanisms for regulatory approval, fee waivers and others - many of which could also apply to AIDS vaccines. The view among participants was that such legislation would appeal most to small biotech companies doing early R & D.

Novel intellectual property and patent agreements also emerged as an area where the EU could make an important contribution. New vaccines are traditionally introduced into industrialized countries and sold at prices intended to recoup the R & D costs - and only then, usually 10 to 15 years later, are they brought into developing countries (at lower prices). One model for avoiding this huge delay is the "social venture capital" arrangements between IAVI and the two "vaccine development partnerships" it supports. The agreement is that IAVI provides funds for the pre-clinical development of vaccine candidates in exchange for an arrangement that allows companies to sell a successful vaccine, if one emerges, at any price in industrialized countries but only slightly above cost in the developing world. Should the latter be impossible for the company, intellectual property rights for developing country markets revert to IAVI, which is free to pursue the most cost-effective manufacturing and distribution paths to keep the price as low as possible.

The EC meeting also discussed other possible actions, including collaboration with developing countries on clinical trials, research on some of the economic and financing gaps in AIDS vaccine development, and public-private partnerships that could accelerate the effort. It was also noted that the EU's 1998-2002 research budget (the so-called Fifth Framework Program) includes US\$65 million for development of four vaccine candidates and related vaccine research. The meeting concluded with the participation of DGVIII's director general, Philip Lowe, who called upon staff to establish an EC-wide AIDS Vaccine Task Force that will formalize and continue the process of defining an EU strategy to promote AIDS vaccines for the developing world. ♦

The Impact of AIDS on Overall Life Expectancy in Selected African Countries



Source: U.S. Census Bureau, World Population Profile, 1998

AIDS Vaccines and Biotech Companies:

An Interview with Therion's Dennis Panicali

Dennis Panicali is president of Therion Biologics Corp., a Massachusetts-based biotechnology company that, since its start in 1987, has been involved in AIDS vaccine development. Before creating Therion, Panicali was a researcher at the New York State Department of Health and then at Applied Biotechnology, Inc. We recently spoke with him about the state of AIDS vaccine development and industry's role in the effort.

IAVI Report: How did you first start working on AIDS vaccines?

Dennis Panicali: I had spent a good deal of time developing poxvirus vectors. We knew these vectors could hold lots of antigen and generate good antibody and CTL responses. So, our approach, from the very beginning, was not very sophisticated – we didn't know what would protect; so we tried to induce broad immune responses by including as many HIV antigens as possible. We called it our “kitchen sink” approach: throw in everything you can, to try and mimic infection.

Many people are talking about that approach today.

Yes. We're still working on this more-is-better approach, but we've also become a lot more sophisticated in making our vectors – not just with vaccinia virus, but also with fowlpox virus and now MVA.

But we still don't have a good handle on which poxvirus is best. My personal belief is that a combination will give us the best possible response. I know the DNA prime/poxvirus boost works well, since we've provided pox viruses to Harriet Robinson [an Emory University researcher who recently reported that monkeys immunized with a DNA/fowlpox combination show some protection against SIV]. But we think we can achieve the same thing with two or three different poxviruses.

Why has it taken so long to figure out which pox virus works best?

Each company has focused on different viruses, so it's hard to compare. Pasteur-Mérieux has focused on canarypox. We've focused on vaccinia. And MVA, which has become the hot approach – the poxvirus du jour. But Therion is too small to carry many programs simultaneously.

How do we decide which vectors to move into Phase III studies without comparing them?

A comparative trial in monkeys is planned. We're making three vectors – identical constructs of MVA, vaccinia, and fowlpox. If you don't use the same promoters and antigens, you really can't compare them. There's also going to be a DNA component in

parallel. We'll look at immunological responses – give a standard boost, and then challenge the animals with a pathogenic SHIV. And Therion is also doing a separate study of prime boosts using two or three poxviruses to learn the best combinations.

The scuttlebutt is that canarypox seems to be a relatively weak vector.

Avipox vectors – both canarypox and fowlpox – tend to give weaker lower immune responses, and unlike vaccinia, they don't replicate in human cells. We're looking at vaccinia and fowlpox vectors in cancer vaccine trials. With MVA, we don't have a lot of comparative data. I think it's somewhere in between the avipox viruses and vaccinia. We still don't know for sure, but my gut feeling is that vaccinia is better than MVA.

Does MVA replicate?

The general belief is that MVA does not replicate in human cells, certainly not to the same extent that vaccinia does.

Is there any real difference between the fowlpox and canarypox vectors?

They're not that different. Pasteur-Mérieux has done a very nice job of engineering canarypox, so it may be a slightly better vector. But we've never done a direct comparison.

Does the route of immunization impact immune responses generated by poxvirus vectors?

It can make a difference. With the non-replicating vectors, intramuscular seems to be a little more immunogenic than subcutaneous. We've also given avipox viruses intravenously, which is by far the best route in animal models. We're testing a fowl pox vector intravenously in a cancer vaccine trial, but there is no data yet.

You were a co-author of Harriet Robinson's recent study. Any thoughts on the study?

It's exciting that these DNA/fowlpox prime boost regimens are showing signs of working. This is consistent with other animal studies. But I believe we've still got to do better – quantitatively and qualitatively. DNA alone is unlikely to get us there. So the poxvirus will be important. I don't think we're at what Harriet calls “protective levels.” But we're getting closer. In other studies, we see lower viral loads and steady CD4 levels in vaccinated monkeys. Some animals appear to be protected, others are not. The challenge is to come up with the right protocol and combination to get near ninety percent protection.

But if you look at the magnitude of the epidemic around

“I would start efficacy trials with what we have now and build on that to develop the next generation of products.”

continued on page 12

the world, the difference between “getting closer” and “being there” is many millions of lives. How can we move things faster?

We have to be willing to take some of these not-quite-optimized vaccines into larger-scale trials. I know the political, economic, social and ethical challenges involved. We have to accept that some products will fail in efficacy trials. We may see protection rates of twenty or thirty percent – which I don’t think is sufficient for wide-scale use.

What level would be acceptable?

It’s got to be above fifty percent, probably higher. But we still don’t know how the SIV or SHIV model compares to HIV infection in humans. As we see more enthusiasm – based on animal studies – we should be ready to move into efficacy trials. If I had unlimited resources, I would start efficacy trials with the products we have now. See how people respond immunologically and build on that to develop the next generation of products. It’s expensive, time-consuming, and fraught with political difficulties. If these 5000-person studies fail, people are going to jump all over you. And where are you going to these trials? Perhaps IAVI can better answer these questions.

What could the U.S. government do to speed things along even faster?

There’s more money out there now. And there’s enthusiasm for approaches like DNA and MVA. It’s just a matter of getting a couple of strong leaders to say, “This looks good, I’ve seen the data, let’s do the trials. And I’ll put my ass on the line and do whatever has to be done to get this trial ready in a year.”

It sounds like you’re describing Don Francis-type people with different approaches.

Yes. And remember, the immune response tests are not a perfected art. That’s very important, because we need reproducible, quantifiable and hopefully standardized assays that can help us move from trial A to trial B.

Your company has been able to raise money for cancer vaccines, but not AIDS vaccines. Why is that?

In the late eighties, people were pretty enthusiastic about an AIDS vaccine. We believed it could be developed by the turn of the century. Biotech was the hot new technology in the investment community. And investors were throwing money into the field. People felt that if you could come up with an AIDS vaccine, it would be a winner. And in 1991, we raised capital on the strength of our AIDS vaccine program. But then the pharmaceutical industry pulled out, because they didn’t think a vaccine was going to happen. It was too difficult and would take too long. And by early 1992, the investment community was saying, “We don’t want

to invest in AIDS.”

So, it wasn’t NIH’s 1994 decision not to go ahead with gp120 efficacy study?

It was way before that. The 1994 decision just put another nail in the coffin. Investors were already getting more sophisticated about all biotechnology products. There were a couple of major failures and money was going into companies that had shorter-term goals. And AIDS is a long-term effort. So we moved into cancer vaccines, because we felt that the technology could generate immune responses – particularly cellular ones – against tumor antigens. We could also attract capital and get a product into the clinic much earlier than with an AIDS vaccine.

But scientifically, are cancer vaccines any closer to showing efficacy than an AIDS vaccine?

We don’t have the same hurdles with cancer vaccines. We have a better sense of the target antigens to go after. The challenge is how to increase CTL levels enough to destroy tumor cells. And we have a good handle on that. We can also evaluate therapies by looking at tumor size or survival, not long-term studies where you must immunize healthy people.

Do you think you could raise private money now, for an AIDS vaccine?

I don’t think so. Not Therion. Don Francis might be able to do it. I don’t know where VaxGen got the money, but he raised a lot. And Genentech put up the initial seed capital. I constantly have to raise money and my investors want to see a product in a few years.

What do you think is the likelihood that VaxGen’s gp120 product will work?

It’s unlikely. I won’t say zero, but from what I’ve seen and know in terms of antibody responses in animals, I don’t think it’s going to work.

You’re also collaborating with Jack Nunberg.

Yes. Jack came to us with his idea of trying to develop a poxvirus vector that can mimic his “fusion competent” immunogen (see page 7). So we’re making pox viruses that express CD4, CCR5, and CXR4. The problem is that the “fusion” is a transient event, which Jack freezes with formaldehyde. If we can find some way to capture this, we’ll get better neutralizing antibodies and it will be very exciting.

But how else could you get good antibodies?

We continue to work on that. In cancer – we’ve got about eight products in the clinic. We’ve been looking at modulating the immune system with different cytokines and costimulatory molecules. And we’re applying what we’ve learned to our AIDS program.

Your company has the rights to Ron Desrosiers’ live attenuated vaccine. Is this approach dead?

I don’t think so. We just don’t understand how to attenuate the

“The investment community has always believed that an AIDS vaccine would make money. But they are not confident that we can develop it.”

virus yet. The simple deletions created a virus that replicates at a low level, and after a long time, something happens that causes problems. Therion is not pushing any human trials. We don't know enough of the long-term consequences.

Have you seen any of Ron's data with the herpes virus vectors?

I like the herpes viruses. The live attenuated vaccines probably protect because of long-term, chronic antigen presentation that causes enhanced immune responses. And herpes viruses may do that in a safer way.

Any other concepts out there that seem interesting to you?

Some of the other vectors look interesting. And IL-12 and other cytokines and adjuvants may help generate stronger responses. I was encouraged by Wyeth Lederle's results using IL-12 to increase CTL responses.

Do you think an AIDS vaccine can make money?

Sure. The hepatitis vaccine makes money. But it took time.

Much of the market for an AIDS vaccine will be in poorer countries. Is this a barrier to investment?

No. Investors have never said that to me. I don't know what the big pharmaceutical companies are thinking, but the investment community has always believed that an effective AIDS vaccine would make money. But they don't have confidence we can develop it. And if it takes another twenty years, investors are not going to see a return. Investors want to know that the company will increase in market value and have liquid stock. And a product twenty years out isn't going to provide liquidity.

Therion at a Glance

Therion Biologics was one of the first companies to become involved in AIDS vaccine development. Since 1987, the Cambridge, Massachusetts-based company, which currently employs 35 people, has evaluated a wide-range of approaches, including poxvirus vectors, live attenuated SIV vaccines, virus-like particles and "fusion competent" poxvirus vectors. Therion's poxvirus vectors are the linchpin of the company's technology for both cancer and AIDS vaccine development. Although the company decided in 1995 to focus primarily on cancer therapeutics, it continues to maintain a research program on AIDS vaccines.

NIH provided Therion with its first grant for work on AIDS vaccines in 1988, and continues to fund much of the company's AIDS vaccine program. In 1998, Pasteur-Mérieux-Connaught agreed to pay up to US\$25 million for commercial rights to cancer vaccines developed by Therion for melanoma, colorectal cancer and lung cancer. To date, only one of Therion's candidate AIDS vaccine has moved into human studies. The vaccine, a vaccinia construct (known as TCB-III), was tested in an NIH-sponsored Phase I study with VaxGen's gp120 used as a boost.

With a cancer vaccine I can get an answer in three years. Maybe the risk is the same – maybe even greater. But it's not going to take me ten or fifteen years. Investing in AIDS vaccines must be compared to other investment opportunities – such as developing new drugs or even Internet companies. People want to see products in three to five years. And the entire biotech industry struggles with that.

So, how do you get companies to invest in AIDS vaccines?

You have to take the risk away. If you say, it's not going to cost you significant dollars, they'll do it. Because they want to. The reason Merck's doing it, I think, is because they really want to develop an AIDS vaccine.

And you may be able to build a platform technology for other vaccines.

Yes. You also use the research in AIDS to help your other programs. But we've got to minimize the risk. It's not liability or market issues. It's just pure, up-front capital investment with short-term horizons. That's where the decisions is made – whether it's a big or small company. The only reason Therion continues to work on AIDS vaccines is because of NIH funding. And we'll always be grateful for that support.

Scientifically, are you more optimistic that an AIDS vaccine is possible?

Much more optimistic. We're seeing better responses and some protection in monkeys from the prime boost combinations. Jack Nunberg has shown us opportunities in terms of neutralizing antibody. So we're making scientific progress. And that pushes all of us to do better because we want to make sure that our vector is the best. We are excited about our next generation MVA, vaccinia and avian pox vaccines, which will be ready next year.

Any safety problems with these pox viruses?

None whatsoever. We've studied vaccinia vectors in over three hundred volunteers, the vast majority in our cancer program who were vaccinia-immune from the smallpox vaccine. We've also tested it in vaccinia-naïve people with no significant side effects. We can administer the vaccine so there is no lesion on the skin. The biggest complication, historically, for vaccinia virus has been the spread to naïve individuals. But with bandaging, or subcutaneous or intradermal inoculation, there is no scab to pick and thus spread. So vaccinia is very safe. And MVA is even safer.

Are there patent problems with MVA?

We don't know. But if we develop a vaccine that works, any intellectual property issues that might arise will be resolved.

A bigger company may have bigger concerns.

Bigger companies tend to be more concerned about certain intellectual property issues. But Therion is not in this for the money. This is not our lead program. We have a technology that we've made available to almost one hundred labs. If we never see a penny from this, it's fine with me. And we're willing to collaborate with any company that gives us a good idea, if we have the resources. ♦

IAVI REPORT

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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.

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GATES GIVES IAVI US\$25 MILLION
continued from page 1

and development, said the new grants will enable IAVI to begin work on up to three new vaccine candidates – one this year, one in 2000, and a third, depending on cost and other variables, in 2001. “We are canvassing the globe for the best scientific opportunities,” Koff said. IAVI is already funding the development of two promising vaccine approaches.

“Thanks to these and other far-sighted donors, we have now raised nearly US\$50 million, a meaningful down payment on the US\$350 to US\$500 million budget outlined in our *Scientific Blueprint for AIDS Vaccine Development*,” Berkley added. The *Scientific Blueprint* lays out a detailed scientific strategy to develop an AIDS vaccine as quickly as possible.

William H. Gates, Sr., who oversees Gates Foundation activities for his son, praised IAVI's goal of making AIDS vaccines accessible in developing countries. “This is very much in keeping with the philosophy of the Bill and Melinda Gates Children's Vaccine Program, which seeks to immunize children in developing countries against vaccine-preventable diseases,” he said. “It would be a hollow victory to save millions of children's lives, only to have them succumb to AIDS. We're persuaded that the strategy of moving multiple vaccine candidates forward simultaneously will yield the fastest results.”

The president of the World Bank, James D. Wolfensohn, said: “I am delighted that the Gates Foundation has stepped in so generously to support IAVI's work to speed up development of an AIDS vaccine. The World Bank has provided seed grants of several million dollars to assist IAVI's start-up, so we are especially pleased to see this strong private contribution by the Gates Foundation further build up IAVI's capacity.”

Ralph E. Gomory, president of the Sloan Foundation, called on governments, multilateral organizations, foundations, and individuals to join in funding IAVI's work. “There is a pressing need for a practical and focused effort like IAVI's,” he said. “Support for IAVI can make a critical difference to a massive worldwide problem that everybody recognizes but few know how to attack in a practical way.”

IAVI is moving quickly to deploy its new resources. “We are convening a scientific think tank in Europe in June to identify promising vaccine approaches,” said Jaap Goudsmit, chair of IAVI's Scientific Advisory Committee and chair of the Department of Human Retrovirology at the University of Amsterdam. IAVI held a similar brainstorming session in New York in April, 1999. ♦

KEYSTONE SYMPOSIA
continued from page 8

by stopping therapy and then starting again. However, he cautions that other patients have done the same thing and have had viral rebounds. Gabriel Orates, also of the Aaron Diamond Center, presented this same data at the Retrovirus meeting.

Bacterial Vectors

Researchers from the University of Siena in Italy reported on a number of bacterial vectors they were studying. One vector, using the bacteria *S. gordon* expressing pieces of HIV and SIV *env* and *gag*, is already in monkey studies. However, the bacteria appears to persist far longer in mice than in monkeys. The Italian researchers are also testing an *E. coli* vector encoding the V3 domain of the envelope.

Yellow Fever/Polio Vectors

A research team from the University of California at San Francisco has created yellow fever and poliovirus vectors expressing HIV and SIV antigens. The two vectors can protect animals against a challenge with an aggressive melanoma cell line but challenge studies have yet to be done in the SIV/monkey model. ♦

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India Launches AIDS Vaccine Program

New estimate of 8 million HIV-infected people in country adds urgency

by Suman Raghunathan

The April, 1999 collapse of India's coalition government could pose a challenge to the country's newly-declared goal of establishing a national AIDS vaccine program. Prime Minister Atal Behari Vajpayee, who will remain in office until elections in September, announced the initiative in a speech at a National AIDS Control Organization Conference last December. Vajpayee declared the development of an AIDS vaccine a top national priority and challenged India's politicians, scientists and industry leaders to join together in a project he accorded "mission-like" status. The speech came as a surprise to many: although India has more HIV-infected people than any other country in the world (the latest estimate is 8 million, according to India's Parliamentary Standing Committee on Dreaded Diseases) – until recently its government had barely acknowledged the AIDS epidemic.

At the time, Vajpayee's unprecedented step gave a major boost to the initiative, says Vulimiri Ramalingaswami, professor and former head of the Indian Council of Medical Research (and member of IAVI's Scientific Advisory Committee), who is involved in its planning. Such top-level commitment held out the promise of new funding and political clout to help overcome the obstacles ahead: India's complex bureaucracy and internal politics that limit collaborations between scientists and industry; its status as a newcomer to HIV vaccine research; and a concern about international collaborations, which are sometimes seen as one-sided and exploitative. Now, says Ramalingaswami, the best hope is for a new government that shares Vajpayee's commitment to an AIDS vaccine for India and can transform the idea into a concrete plan.

Since Vajpayee's announcement, Ramalingaswami and several other researchers have been working to define the vaccine project's goals and strategies. The effort will be organized into three branches. The first will comprise the scientific program and overall coordination, and is slated to include researchers from the Indian Council of Medical Research, the federal Department of Biotechnology, and the National AIDS Control Organization. The Indian pharmaceutical industry forms the second branch, and the third will consist of international collaborators. Teams of people from the different branches will be formed as needed to work towards the program's specific goals.

The crucial decision for India is the choice of which vaccine candidates and concepts to pursue. At present, emphasis is on two approaches: modified vaccinia vectors (MVA) and DNA vaccines, with projects in the works at several sites around India and focusing on clade C, which accounts for roughly 80% of HIV infections in the country. Further work will continue research on exclusively Indian vaccines and on modification of promising non-clade C prototypes developed internationally. Some of the funding will come from the World Bank, which is poised to continue its support of a broad-based Indian AIDS program with a US\$191 million low-interest credit now under consideration for 1999-2004.

But even with a scientific strategy in place, the program faces an uphill battle. One major challenge will be to cut through India's bureaucracy and the inertia endemic to its government research

institutions – areas where top-level political support could be crucial, as it was for India's other national "mission-status" successes in developing super-computers and nuclear weapons. Another important task will be to develop a larger cadre of researchers who can carry the science forward, which is likely to involve training abroad through mechanisms such as the Indo-U.S. Vaccine Action Program (VAP). Launched in 1987 to facilitate joint projects for fighting respiratory diseases, the VAP added HIV vaccines to its mandate in 1997 and could become a key resource for establishing technology transfer systems to feed the HIV vaccine program.

Projects like the VAP demonstrate that India can work effectively with foreign scientists, despite some residual mistrust of international collaborations. Building on this trend could prove crucial to India's vaccine program, says Peggy Johnston, assistant director for AIDS Vaccines at the U.S. National Institute of Allergy and Infectious Diseases, since it will help India incorporate the best vaccine candidates and technologies based on their scientific merit – regardless of where they originate – rather than on nationalistic considerations.

The vaccine program's blueprint also calls for technology transfer between India's research centers and its pharmaceutical industry. "Opportunities for involvement will shift incrementally toward industry as time moves on in the vaccine development process," says Ramalingaswami, since companies will have the pivotal role of optimizing the best candidates, along with manufacturing and eventually distributing them. The Indian pharmaceutical industry has a great deal of experience in these areas: several companies have World Health Organization-certified GMP facilities that produce and distribute vaccines to more than 130 countries. But for this transfer to work effectively, Ramalingaswami adds, industry must be involved in the HIV vaccine program from its outset – which means a major shift in how research generally operates in India, where industry traditionally remains on the sidelines.

Work is also underway to build an infrastructure for conducting clinical trials of HIV vaccines. India already has considerable experience with large-scale vaccine testing, and recently concluded two efficacy trials – one for leprosy, as part of a WHO project, and the other for BCG (as a tuberculosis vaccine). For HIV trials, one cohort of commercial sex workers has already been assembled in Pune, while another (of intravenous drug users) is being organized in the state of Manipur. In addition, India's Human Rights Commission is formulating a set of ethics guidelines for clinical trials and will release them soon for national discussion. Communicating clearly why a vaccine is necessary, along with information on how trials will work, will be essential for winning public support and "dispelling the guinea-pig syndrome," says Ramalingaswami. That is no simple task in a country of almost one billion people where, like many places in the world, AIDS is still a taboo subject and many perceive their risk of infection as very low. But it will be crucial to harness the collective will if India is to make progress in fighting one of its deadliest challenges ever. ♦

planned reorganization of its vaccine trials program, and the new product development team program which will fund 1 to 5 teams at a total of up to US\$10 million per year.

Japanese AIDS Vaccine Program

Mitsuo Honda of the Japanese National Institute of Infectious Diseases provided information on Japanese efforts to develop an HIV vaccine. Overall, the agency is focusing on the development of BCG vectored vaccines, gp120 and DNA vaccines. The BCG vectored vaccines include pieces of *env* (from subtypes B and E), *nef*, *pol* and *gag*. Honda also discussed preliminary data on antibody and cellular responses induced by the BCG vaccines, along with plans for clinical trials in Thailand.

Immune Responses to HIV

Debbie Birx of WRAIR reviewed immune responses to HIV infection and vaccination, and discussed new studies in highly-exposed persistently seronegative individuals (called HEPS) who show HIV-specific CTL responses and mucosal IgA responses. Birx reported that only 27% of people with cellular (T-helper) responses to clade B vaccines showed cross-reactive T-helper responses to clade E. In both HEPS and exposed but persistently seronegative macaques, protection appears to be associated with IgA (a type of mucosal antibody), rather than systematic IgG responses.

Listeria, Anthrax Toxins as HIV Vaccine Vectors

Harvard's Judy Lieberman discussed two new vaccine strategies and a lab assay under development that might be able to predict whether vaccines will stimulate CTL responses. In collaboration with Fred Frankel at the University of Pennsylvania, Lieberman is studying attenuated listeria as a bacterial vector vaccine. Since listeria can cause disease in immunosuppressed individuals, Frankel has attenuated the bacteria by deleting some key genes. Oral immunization with a listeria (expressing HIV *gag*) induces mucosal CTL responses and protects against vaccinia-*gag* in infection mice. Lieberman reported that the listeria vaccines gave the highest CTL levels of any vaccine strategy she has evaluated in mice. In collaboration with Yichen Lu of Avant Immunotherapeutics (a Massachusetts-based biotech company formed by a merger of T-Cell Sciences and Virus Research Institute), she is also evaluating the potential of an anthrax toxin, in which the toxin is removed and replaced by HIV epitopes to stimulate CTL responses. Finally, Lieberman is developing an assay she hopes will predict the ability of candidate vaccines to elicit HIV-specific CTLs in humans.

AIDS Vaccine Research in Thailand

A series of speakers addressed issues related to conducting HIV vaccine trials, including the roles of monitoring committees, host countries and sponsoring organizations and long-term follow-up of vaccine trial participants.

Several speakers described the extensive clinical trials infrastructure developed in Thailand since the start of HIV vaccine testing in 1994. Natth Bhamarapravati discussed the organizational structure and roles of the national committees. Chatapong Wasi reported on surveillance and monitoring of HIV isolates in Thailand; Praphan Phanuphak discussed establishment of facilities to produce candidate vaccines.

Sample repository and data management issues were also described.

Sorachai Nitiyapan of the Armed Forces Research Institute for Medical Sciences reviewed data from Phase I and II trials of Chiron's gp120 vaccine. The 0,1,6 month immunization schedule proved superior to the 0,1,4 schedule; 95% of the subjects generated neutralizing antibodies to the laboratory strains of HIV, but none to primary clinical isolates of HIV. In the Phase II, 400-person trial of a bivalent gp120 (made from Thai E and clade B subtypes), no volunteer neutralized the clade E strain used to produce the vaccine.

Wyeth's HIV DNA Vaccines

David Weiner reported on the University of Pennsylvania's DNA vaccine program. (Wyeth-Lederle, which recently purchased Apollon, holds the intellectual property rights to the Penn research.) Plasmids consisting of *gag-pol*, *env* genes from clades A-E, and some HIV regulatory genes have been evaluated in mice, non-human primates, and in preliminary clinical trials (*env-rev*). Higher doses of DNA were needed for monkeys compared with mice; antibody responses were much lower in primates than in mice; the higher doses of DNA induced CTLs. Current Phase I DNA vaccine trials include studies of the *gag-pol* and *env-rev* constructs at NIH and the *env-rev* construct at WRAIR and at Penn. Wyeth is now looking at strategies to improve the immunogenicity of DNA vaccines, including the use of cytokine genes and co-stimulatory molecules.

Gallo on Vaccines

Robert Gallo of the Institute for Human Virology in Baltimore reviewed data suggesting a role for the chemokines MIP-1 alpha, MIP-1 beta and RANTES in protecting against HIV, including epidemiologic data from a cohort of hemophiliacs exposed to HIV in the early 1980s and followed for several years. A small percentage of the cohort was not infected with HIV, and this correlated with levels of these chemokines. Gallo also discussed the role of glycosaminoglycan (GAG), a sugar on the cell membrane, which may play a role (along with certain co-receptors such as CCR5) in activating the cell response to the chemokine. The chemokine-sugar complexes increase antiviral activity compared with chemokines alone. He noted that interferon-alpha (IFN) and HIV *tat* may play a significant role in HIV-induced immunosuppression, and that he and Daniel Zagury are focusing on ways to block IFN-alpha and *tat*. Fourteen HIV-negative volunteers have received an HIV *tat* vaccine, and the researchers plan to include the *tat* gene with other vaccine approaches in the near future. Finally, Gallo noted that two recent studies have shown that candidate vaccines utilizing the regulatory genes can protect monkeys: Italy's Barbara Ensoli *tat* construct and Dutch researcher Albert Osterhaus's *rev/tat* construct in an alphavirus prime, MVA boost study.

Immune Responses to Whole Killed HIV

A group of researchers from the U.K, Thailand and the U.S. presented work on the immunotherapeutic effect of a whole inactivated HIV vaccine (Remune®) developed by the Immune Response Corp. (IRC). Remune is a gp120-depleted, whole-inactivated HIV vaccine derived from a clade A/G recombinant virus, which is killed with chemical and radiation treatments. IRC is exploring the issue of evaluating Remune in uninfected subjects as a preventive vaccine and as a booster for other vaccine strategies that target cell mediated immune responses (see *IAVI Report*, January-March 1999). ♦