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IAVI REPORT

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Paris Meeting Spotlights Renewed Focus on Antibodies

by Patricia Kahn

On 5-6 May 2000, the Institut Pasteur, with the sponsorship of French and American research agencies, hosted a workshop in Paris on HIV/AIDS vaccine development. The workshop was the second in an annual series sponsored by France's Agence Nationale de Recherche sur le SIDA (ANRS) and the U.S. National Institutes of Health (NIH), with additional sponsorship this year from UNAIDS, and is slated to alternate between the two continents. While no major new findings were reported, the conference reflected a distinct trend in the field: the resurgence of interest in antibodies, an area that has seen less attention over the past few years as HIV researchers increasingly focused on cellular immunity as the key to protection. The meeting also featured roundtable discussions on issues such as HIV vaccine trial ethics and strategies for vaccine development and deployment.

The opening session began with Philippe Kourilsky, director of the Institut Pasteur (and former head of research at Pasteur-Mérieux-Connaught), who gave his view of the top priorities to address. One is to explain why animal models do not always predict how a candidate HIV vaccine will work in humans, knowledge which could help researchers improve the usefulness of these model systems. Others are to establish clear criteria for deciding

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IAVI Launches Project to Develop Oral HIV Vaccine

by David Gold

On 18 May 2000, IAVI announced that it is forming a partnership with the U.S.-based Institute of Human Virology (IHV) and the Ugandan Ministry of Health to develop an orally administered HIV vaccine. The announcement was made in Baltimore by leaders of IAVI and IHV, along with Uganda's Director General for Health.

Researchers at IAVI and IHV, a center of the University of Maryland Biotechnology Institute founded by U.S. researcher Robert Gallo, believe that the new vaccine could be produced and sold for far less than other HIV vaccines currently in the pipeline. IAVI is committing at least US$3 million over three years to complete initial development of the vaccine.

At the same time, IAVI announced that it has formed a partnership with the Ugandan Ministry of Health to work with several scientific institutions there on further development and testing of this and other IAVI-sponsored HIV vaccine candidates.

The new partnership will use a bacterial vector to deliver an HIV DNA vaccine. In developing this approach, researchers genetically altered a strain of Salmonella bacteria to make it safer and able to carry the HIV DNA vaccine. In an example of how IAVI plans to use its vaccine development partnerships (VDPs) to support one another's research efforts, the DNA vaccine to be

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VACCINE BRIEFS

Uganda Canarypox Trial Completes Immunizations
Scientists from the Joint Clinical Research Centre in Uganda reported that they have completed all immunizations of the first HIV vaccine tested in Africa, the canarypox-based vDP205. Each of the 40 volunteers in this Phase I trial received four injections and will continue to be observed for at least one year after the last injection.

"Worst Epidemic Ever" in Central America
"The HIV epidemic in Northern Honduras could approach the catastrophe of sub-Saharan Africa," according to Carlos Lopez, executive director of Fraternidad San Pedrana le Lucha Contra el SIDA, Honduras' largest private AIDS organization. Lopez estimates that 520,000 Hondurans are now infected with HIV and that "HIV infection in the city of San Pedro Sula alone could be as high as 240,000 – nearly half the residents. I believe that this is the worst health epidemic in the history of Central America," he added. Still, doctors and officials disagree on the extent of the epidemic, as the government did not begin to track cases until this year. According to estimates by the Health Ministry's AIDS program, about 40,000 Hondurans are HIV-positive.

Thailand VaxGen Trial 80% Enrolled
Researchers at VaxGen report that their Phase III HIV vaccine trial in Thailand has enrolled more than 2,118 of the 2,500 volunteers needed for the study. The candidate vaccine is based on gp120 from the B and E subtypes of HIV. It is also being tested on 5,000 volunteers in North America and Europe.

In March, Thai Public Health Minister Korn Dabbaransi reported that the number of HIV infections in that country was expected to reach one million by the end of 2000. Thailand began trials of candidate HIV vaccines in 1993 and to date, 10 different trials have been approved in the country.

Paying People to Get Vaccinated: One Strategy for Reaching the "Difficult-to-Access"
As more attention is focusing on how to deliver an HIV vaccine once it is developed, some researchers are looking to existing vaccines for lessons. Public health officials have long known that distributing a vaccine to high-risk adults, even in wealthy industrialized countries, poses significant challenges. In a paper published in the *American Journal of Public Health* (March 2000), researchers from the Intravenous Drug User Project in Anchorage, Alaska, describe how they successfully vaccinated high-risk, difficult-to-access groups like injection drug users (IDUs) against hepatitis B. The researchers recruited IDUs from the streets and referred them to vaccination centers, but only 7% of 140 users received the first hepatitis B shot. However, when a financial incentive (US$10) was offered for proof of vaccination, 48% of 172 users got vaccinated.

New Report on Epidemic in South Africa
More than 3.5 million people in South Africa are infected with HIV and this number is expected to more than double over the next decade, according to a newly-released report commissioned by loveLife, a South African program dedicated to adolescent sexual change behavior, and funded by the Kaiser Family Foundation.

"The Impending Catastrophe: A Resource Book on the Emerging HIV/AIDS Epidemic in South Africa" warns that the country's 15-25 year olds are "the most severely affected," with infection rates as high as 60%. It also offers detailed analysis and data on the disease's impact on South Africa's health, economic and social systems. The report was prepared by Abt Associates South Africa Inc.

The executive summary and full report are available online at the Kaiser Family Foundation website (www.kff.org) and the loveLife website (www.lovelife.org.za).

UNAIDS Releases Ethical Guidelines
In May 2000, UNAIDS released a guidance document, "Ethical Considerations in HIV Preventive Vaccine Research". The report specifically addresses issues arising in developing countries, where many future vaccine trials are expected to take place. Peter Piot, executive director of UNAIDS (and a member of IAVI's Board of Directors) said, "In the long term, a vaccine may offer the best hope of controlling the AIDS epidemic, especially in developing countries. It is our collective responsibility to ensure that all vaccine trials are conducted under the strictest possible ethical and scientific standards."

The document took more than two years to develop and is based on a series of consultations organized by UNAIDS with representatives from 33 countries (see *IAVI Report*, April-June 1999). The most contentious issue concerned the level of treatment that should be offered to participants who become infected with HIV during the course of the trial. According to the UNAIDS document, "Care and treatment should be provided, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country."

The full report is available at the UNAIDS website (www.unaids.org).

Phase II "Prime-Boost" Trial to Begin in Brazil, Haiti, and Trinidad

by Sam Avrett

A consortium of vaccine trial sites in Rio de Janeiro, Port-au-Prince, and Port of Spain will begin enrolling volunteers in June 2000 for a Phase II HIV vaccine trial. Planned since March 1998, it will be the first international multi-site Phase II trial of a preventive HIV vaccine, and only the fourth Phase II preventive HIV vaccine trial ever conducted.

Funded by the U.S. National Institutes of Health (NIH), the trial will enroll 120 people, 40 at each site. The research protocol received final approval from nearly all governmental and institutional review boards in late March (with a decision from Trinidad and Tobago's AIDS Vaccine Ethics Committee still pending as the *IAVI Report* went to press). All three sites are now making final preparations for enrollment.

The trial will evaluate a "prime-boost" combination HIV vaccine with two components: a canarypox vector (vCP1452, manufactured by Paris-based Aventis Pasteur) carrying multiple genes from an HIV subtype B strain, and an envelope protein fragment (gp120MN, produced by VaxGen of San Francisco) from a lab-adapted, B subtype-derived strain. Its main goal is to generate more data on the safety and immunogenicity of the canarypox vector, alone and in combination with the envelope subunit vaccine. It will also raise the level of operational experience in conducting an international multi-site trial, including the collection of data and laboratory samples, building laboratory capacity, and recruiting populations for HIV vaccine trials, all of which may pave the way for future HIV vaccine trials in these countries. (A Phase III trial of canarypox plus gp120 is now under consideration by leaders of the NIH-funded Vaccine Trials Network.)

According to research staff at the sites, the major challenge in preparing for the trial was the political process rather than the science. "There was a remarkably solid basis of collaboration and support among the team of researchers from Brazil, Haiti, Trinidad and Tobago, the U.S. NIH and Family Health International," said Trinidadian researcher Farley Cleghorn, "and this allowed planning to go very smoothly. Yet the approval processes within our own country and in others took a year to complete." Mauro Schechter, principal investigator of the Rio de Janeiro site, described a similar experience. "By and large, most people at the various Brazilian agencies tried to be helpful, and because AIDS touches everyone, most government officials understood the need for this research," he said. "But, since this is the first international multi-center trial, often officials were not able to tell us precisely what approvals and documents were needed, and from which ministry or agency. Now we know our way through the maze."

Community groups in all three countries were involved early in planning for the trial. "Our community advisory board reviewed and commented on the protocol and informed consent forms, and we will be glad to see this trial finally enrolling," said Alexandre do Valle Menezes, head of the Rio PWA group, Grupo Pela Vidda.

The trial will randomize 120 participants into three groups: 45 participants to receive three doses of the combination of vCP1452 plus gp120MN (by intramuscular injection), 45 to receive three doses of vCP1452 only, and 30 to receive placebo. The trial volunteers will be mostly heterosexuals at low risk for HIV, along with some homosexual men at the Brazilian site. In addition to producing more immunogenicity data on these vaccine products, the trial will collect data on whether host factors such as HLA type, nutritional status or concurrent infections affect the immune responses generated by these vaccines.

The vCP1452 construct is the latest refinement in a series of canarypox vectors developed by Aventis Pasteur. Containing parts of HIV-1 genes *env*, *gag*, *pol*, and *nef* together with vaccinia promoter sequences that boost gene expression, vCP1452 has already been tested in approximately 50 volunteers and has shown no safety problems. Preliminary data from a U.S.-based trial (AVEG 034) with 90 volunteers indicate that vCP1452 elicits significantly higher levels and frequencies of cellular immune responses than two other canarypox products (vCP1433 and vCP205), although vaccinees are still being followed so these results are not yet final. In total, canarypox-based HIV vaccine candidates have been tested for safety and immunogenicity in nearly 1,000 people in the U.S., France, and Uganda.

The subunit gp120MN envelope protein is a VaxGen product that pre-dates their bivalent gp120B/B1qaz product now in Phase III trials in the U.S., Thailand, and the Netherlands. Derived from an early subtype B strain that was adapted to grow in cultured cells, the gp120MN protein has been tested for safety and immunogenicity in approximately 1,300 volunteers in the U.S. and Thailand.

The clinical trial sites for the current international Phase II trial are the Hospital Escola São Francisco de Assis in Rio de Janeiro, Brazil; the Institut National de Laboratoire et de Recherches in Port-au-Prince, Haiti; and the Medical Research Foundation in Port of Spain, Trinidad. ◆

Sam Avrett was the founding executive director of the AIDS Vaccine Advocacy Coalition.

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which vaccine candidates should move into clinical trials, and to identify correlates of immunity. He also called for establishing "emergency procedures" to cut through the regulatory bureaucracy in France and some other countries, so that clinical trials of HIV vaccine candidates can be launched more speedily.

The theme of unresolved challenges was also taken up by Neal Nathanson, director of NIH's Office of AIDS Research, who pointed out that researchers have not identified correlates of immunity for any of the licensed vaccines that are widely used today. "Once a vaccine works, scientists tend to walk away from it and leave it to the public health community to deploy," he said. "If we'd used these opportunities to figure out how some of these vaccines work, and the correlates of immunity, we'd be way ahead now."

Interest in antibodies has been rekindled by passive protection studies and a wealth of new information on envelope proteins.

Jose Esparza, coordinator of the WHO/UNAIDS HIV Vaccine Initiative, gave a brief update on the global AIDS epidemic. Although first identified only 20 years ago, HIV is now the leading cause of death in Africa and the fourth biggest killer in the world, with over 2.5 million deaths (and 5.5 million new infections) in 1999 alone. In at least 15 countries, over 10% of the population is infected with HIV. Esparza finished by saying that only a vaccine can end the epidemic, and "without Phase III trials we will never get one."

The HIV Envelope and Neutralizing Antibodies

Quentin Sattentau of the Imperial College School of Medicine in London gave a concise overview of research on the HIV envelope protein, and reviewed efforts (mostly unsuccessful so far) to generate antibodies that neutralize field isolates of HIV. He began by pointing to the re-emergence of interest in antibodies after years when many researchers 'lost confidence" that humoral immunity had a useful role to play in protection against HIV, an attitude he attributed to the field's "mistake of relying on lab strains of HIV." (Lab strains have a more flexible envelope structure than field isolates and are therefore much easier to neutralize.) But interest has been re-kindled by the recent demonstrations that high levels of neutralizing antibodies (given passively) can protect monkeys against HIV, and by the better strategies possible now that the atomic structures of gp120 and gp140 have been solved.

Sattentau then described why HIV is so difficult to neutralize. A prime reason is that gp120 is one of the most heavily glycosylated proteins known, with the sugar molecules on its surface acting as an "antigenic shield" that masks potential neutralizing epitopes underneath. The gp120 outer loops are also highly variable and immunodominant, and therefore deflect immune responses away from more conserved epitopes in the molecule's core.

Yet Sattentau called the present time a "very optimistic period," pointing to the variety of approaches now being taken to circumvent these problems and generate antigens that induce neutralizing antibodies. Jack Nunberg and Peter Kim, among others, have proposed that conformational changes in the envelope protein (during HIV entry into host cells) transiently expose some buried, potential neutralizing sites, an idea that has spawned many efforts to capture and stabilize these sites. Some investigators are modifying envelope proteins (for example, by stripping off sugars or deleting regions such as the V2 hypervariable loop), while others are attempting to stabilize them in their native oligomeric form, rather than using monomeric gp120 as a vaccine antigen. Other approaches involve novel antigen-presenting systems, such as dendritic cells and new types of adjuvants.

Protection by Antibody Infusion

Ruth Ruprecht of the Dana Farber Institute gave an update on her recently-published study showing protection of newborn macaques via antibodies (*Nature Medicine*, Feb. 2000, p. 200). In that work, she infused animals just before and after birth with a mixture of three broadly neutralizing monoclonal antibodies against epitopes in the envelope protein, and then challenged them intrarectally with a low-pathogenic SHIV strain (SHIV-IIIB). (In that study, the mothers were also protected against an intravenous challenge.)

Given the potential of this approach as a treatment to block infection (from mother-to-child and in post-exposure prophylaxis), Ruprecht has now extended these studies. Here she reported on a simpler regimen that eliminates the three pre-natal infusions and instead uses only two treatments (given to infants one hour before and 8 days after challenge) and challenged animals orally with a more pathogenic strain (SHIV89.6P). In a small preliminary study involving four treated and four control animals, she saw complete protection in one of the vaccinated infants and partial protection in 2 (which became infected but showed a delay of CD4+ cell loss and death, and a 20-50-fold blunting of viral load). The fourth vaccinated animal became infected and died rapidly, similar to the four untreated controls.

IgA and Immunity in "HIV-Resistant" Women

Women who are highly exposed to HIV but remain seronegative (ESN) have been intensively studied by immunologists, with most of the attention on their circulating HIV-specific cellular responses (especially CD8+ killer T-cells). Two talks at the meeting focused on the less-studied immune responses in the mucosa, building on earlier studies (by Sandra Mazzoli and Mario Clerici, and by Rupert Kaul) showing that ESN are much more likely than infected women to have HIV-specific IgA antibodies in their genital secretions.

First, Lucia Lopalco of the San Raffaele Scientific Institute in Milan reported identifying an epitope that seems to be recognized only by IgA from ESN (4/6 individuals). This finding emerged from a study comparing epitope specificities of serum IgA (which reflect the mucosal IgA repertoire) from ESN and HIV-infected people. The epitope mapped to a four amino acid stretch (aa 581-584) within the molecule's "coiled coil" region – a region well-known through the work of Peter Kim for its key role in viral entry and as a new anti-HIV drug

target. Mouse antisera that recognize this epitope blocked HIV entry and replication in laboratory tests, results consistent with the idea that antibodies directed against this epitope may mediate HIV neutralization in ESN women and contribute to their resistance to HIV infection.

Michel Kazatchkine of the Université Pierre et Marie Curie presented a study by colleague Laurent Bélec, who screened cervico-vaginal secretions from 342 ESN sex workers in Abidjan and found 25 (7.5%) with anti-HIV antibodies (IgA, IgG and IgM). Before analyzing them for their possible role in protection, the researchers eliminated all samples (15 out of 25) that contained either semen or a Y chromosome, since antibodies in these cases might have originated from the ESN female's sex partner. The remaining ten samples reacted predominantly with a known neutralizing epitope in gp41 (different from Lopalco's, but identical to that recognized by Ruprecht's anti-gp41 neutralizing monoclonal antibody, 2F5). Antibodies purified from these samples blocked the movement of cell-associated HIV through tight monolayers of cultured epithelial cells, which the researchers hypothesized might reflect an ability to restrict "transcytosis" of HIV through the mucosa and into the epithelial cell layer in ESN women.

Enhancing antibodies

The first roundtable session had several presentations on a less welcome aspect of antibody function: immune-mediated enhancement. Jay Levy of the University of California at San Francisco began by citing the classical example of enhancing antibodies in Dengue fever. In this mosquito-borne disease, prior infection with one serotype of the virus can lead to more severe disease after infection with another one, due to the presence of antibodies that actually help virus enter host cells (via Fc or complement receptors). Levy then raised the question of whether some candidate HIV vaccines might worsen or accelerate disease, since he and others have detected HIV-specific antibodies (in blood from some infected or vaccinated people) which lead to increased levels of viral replication *in vitro*. In one case, blood from a person who became infected after vaccination with a gp120 vaccine (made from an HIV-SF2 strain) had antibodies that neutralized SF2 *in vitro* but enhanced infection of cultured cells with African or Haitian strains. Levy's lab also showed that a monoclonal antibody to the V3 loop neutralized HIV-SF2 but increased replication *in vitro* of a variant differing in only one amino acid.

Next, Ron Montelaro of the University of Pittsburgh gave an overview of what has been learned from vaccine work on the equine infectious anemia virus (EIAV), a talk he subtitled "A Little Horse Sense in HIV Vaccine Research." Like HIV, EIAV is a lentivirus, causing a chronic immunodeficiency disease in horses that starts with acute infection, usually followed by recovery and then repeated cycles of sickness continuing for up to one year – each time with a different variant of the virus. Researchers have tested a wide range of vaccine designs and found two effective ones (whole killed and live attenuated), several that give partial protection (particle-based vaccines), and others that sometimes enhance disease (viral and recombinant envelope subunits). (Similar results were seen with experimental FIV vaccines in cats.)

Focusing on enhancement, Montelaro said that 9/17 horses

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Enhancing Antibodies: A Concern for HIV Vaccine Trials?

Do HIV-specific enhancing antibodies in the blood of some infected people and vaccinees presage a risk to trial volunteers? While that question appeared to be new to many workshop attendees of the roundtable session on "Potential Problems in HIV Vaccine Development" (see main article), enhancing antibodies are actually an old, familiar topic in vaccine science.

They are also ubiquitous: nearly all families of enveloped viruses induce antibodies that can lead to increased virus replication *in vitro*, including some for which vaccines have been safely used in millions of people, such as yellow fever and Japanese encephalitis virus. Yet enhancing antibodies can clearly worsen disease in some cases, such as Dengue fever and the immunodeficiency in horses caused by the equine infectious anemia virus (EIAV), where they also raise viral load.

The problem, according to Duke University's David Montefiori – one of the immunologists who first identified HIV-specific enhancing antibodies in 1988 – is that no *in vitro* test can predict which enhancing antibodies will affect disease and which ones are harmless. So Montefiori, a principal investigator of the central immunology laboratory for NIH-sponsored AIDS vaccine trials, has combed the literature for data that might point to disease enhancement, either in the many SIV experiments done in monkeys, or with HIV in humans.

So far, he's found none. "There's no evidence that these antibodies have a negative impact *in vivo*," he says. "The broad picture is almost overwhelmingly that these [experimental] vaccines haven't made things worse."

Yet Montefiori points out one still-open aspect of the question. Besides worsening the course of disease, enhancing antibodies could (in theory) make viruses more infectious, which for HIV would translate into increased susceptibility to infection. This has been documented only rarely, for example, in the rather exotic Aleutian disease virus of mink, where it was specifically looked for. But the possibility has not been ruled out by existing monkey data, largely because it has not been explicitly investigated. Such experiments would require large numbers of monkeys to be vaccinated and then given suboptimal virus doses, which is both difficult (due to shortages of monkeys for research) and expensive to do.

So, while results with SIV in monkeys are reassuring so far, he says, "I will feel comfortable if there is no increased rate of transmission in the VaxGen trial. Then we will probably have nothing to worry about." He calls the trial "pivotal" in addressing this issue, and sees its results on transmission an "under-recognized benefit of the trial." ◆

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given a recombinant envelope gp90 subunit vaccine and then challenged with homologous virus (the one used to make vaccine) showed signs of more severe disease, while 5 had the typical disease course and 3 showed some protection. One animal died within two weeks after a challenge with heterologous virus (of a different strain), something that rarely happens, with a viral load 100-1000 times higher than that in unvaccinated animals. Yet antiserum from that horse caused less than a 2-fold increase in viral replication *in vitro*, showing that this assay does not reflect disease-enhancing potential.

Other studies on the EIAV system have used these different types of vaccines to look for correlates of protection. Montelaro said that no single parameter emerged as a reliable correlate, although there was a general trend towards better protection with more mature antibodies (those with higher avidity and conformational dependence, which appear later in a humoral response). That led to his conclusion: HIV vaccine designs should aim at accelerating antibody maturation, using approaches such as sustained antigen presentation or prime-boost regimens that seem to drive maturation forward more rapidly.

Pierre Sonigo (Institut Cochin de Génétique Moléculaire, Paris) also spoke about enhancement of infection in animals, in this case with DNA vaccines against feline immunodeficiency virus (FIV). But these vaccines do not induce antibodies, which means that there must be other factors that can lead to enhancement. Further studies (not in the FIV system) showed that one such factor is IL-12, a cytokine made after immune stimulation. That result suggests a paradox: immune activation (with release of cytokines) is necessary to generate protective responses, but may also contribute to enhancement. Sonigo concluded that antibody function reflects a balance between enhancement and protection.

The session ended with some concern in the air over whether HIV vaccines could lead to disease enhancement, but no additional *in vivo* data emerged from the question-and-answer period. (For further discussion, see "Enhancing Antibodies - A Concern for HIV Vaccine Trials?," page 5. For comprehensive reviews on enhancement, see Mascola et al., AIDS Research and Human Retroviruses 9, 1175, 1993; Burke, Perspectives in Biology and Medicine 35: 511, 1992.)

Making better antigens

The remaining talks on antibodies presented various strategies for making better antigens, work mostly in very early stages. Indresh Srivastava of Chiron (Emeryville, California) described the company's studies comparing oligomeric envelope (gp140) with monomeric gp120. Both proteins can be mass-produced and purified in what look like authentic versions (based on glycosylation patterns, CD4- and antibody-binding patterns); in rabbits, the gp140 elicits high-avidity neutralizing antibodies

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IAVI Convenes Task Force on Neutralizing Antibodies

On 27 April 2000, IAVI convened the first meeting of a newly established Vaccine Design Task Force on HIV Neutralization. Members of the task force are internationally recognized for their contributions to HIV immunology, structural biology, epidemiology, assay development and vaccine development, and include Dennis Burton, Marc Girard, Guido van der Groen, Carl Hanson (Chairman), Bart Haynes, John Mascola, Quentin Sattentau, Robin Weiss and Richard Wyatt. The group's goals are to review potential vaccine designs aimed at neutralizing HIV (an immune response involving antibodies that bind to viral particles in the blood and block them from infecting cells), and recommend to IAVI's Scientific Advisory Committee approaches with the greatest potential for eliciting such a response.

It is still unknown precisely what type of immune response(s), if any, will protect people against HIV. But in the absence of this information, it is widely assumed that vaccines which induce broad, long-lasting responses in both the cellular and humoral (antibody-based) arms of the immune system offer the best chance of success. Yet none of the vaccines now being tested in clinical trials have been reproducibly effective at neutralizing the highly diverse HIV subtypes circulating in the world today. IAVI has placed high priority on ensuring development of an effective vaccine for use in the developing world, where the AIDS epidemic has hit hardest. For these reasons, efforts are focused on identifying and fast-tracking vaccine strategies that might stimulate different components of the immune system and which, in combination, could elicit broad, durable protection.

The Task Force began by reviewing AIDS vaccine designs focused on HIV neutralization, with emphasis on new envelope glycoprotein designs such as oligomeric and trimeric structures, genetically modified glycoproteins, native immunogens, novel epitopes in gp120 and gp41 and mimotope development to broadly reactive monoclonal antibodies. In future meetings, the Task Force will focus on viral-host cell antigenic complexes, host cell-specific antigens, adjvuants for potentiation of neutralizing antibody responses, and strategies for rapid design and assessment of new and improved HIV candidate vaccines. ◆

Wide Range of Issues Discussed at the 3rd Conference on Vaccine Research

by Pat Fast

The Third Annual Conference on Vaccine Research, held on 30 April-2 May 2000 in Washington DC, included data on a broad range of vaccine-related topics from polio eradication to pre-clinical studies of new vaccines in development.

A number of presentations addressed different ways to deliver vaccines including by intranasal, oral, intradermal (applying it to the skin) administration or using a "jet injector". Needle-less injections have great practical advantages, particularly in terms of mass immunizations. The best example is the current polio eradication campaign, which utilizes the oral polio vaccine. (2000 is the target year for eradicating this disease.) The vaccination of 147 *million* people in India in one day is an extraordinary example of the power of a true national commitment to disease eradication.

On a more sobering note, a resurgence of measles, which was seen recently in Latin America, is an example of how the failure of even one relatively small group to fully commit to disease eradication can put an entire continent at risk.

The conference opened with two talks on the economics of vaccine development and distribution. Amie Batson, of the World Bank's Human Development Network, described efforts of the World Bank, UNAIDS, the Bill and Melinda Gates Foundation, IAVI and others to develop "Push" and "Pull" mechanisms to stimulate HIV vaccine development. ("Push" mechanisms include funding or creating incentives for research and development, while "Pull" mechanisms, which include vaccine purchase funds, are designed to create a market for vaccines once they are developed.)

A number of participants noted that HIV "vaccinology" is beginning to become more integrated into the larger world of vaccine research, development and delivery.

Batson pointed out that as long as many existing vaccines are not purchased and distributed globally, it will be difficult, if not impossible, to convince vaccine manufacturers that an HIV vaccine can be distributed worldwide. For example, the *H. influenzae* type B (HiB) and Hepatitis B vaccines are highly effective against diseases that kill large numbers of children and adults, yet they are unavailable to much of the world.

Michel De Wilde of Aventis Pasteur described the significant investment vaccine manufacturers incur at different stages of development. Research and development costs can now reach into the tens of millions of dollars for pre-clinical work and total more than US$300 million after manufacturing scale-up and registration with regulatory authorities. In the view of many at the conference, the costs of licensing vaccines have been largely underestimated.

De Wilde described a typical dilemma within a company: the decision to initiate efficacy trials and commit to the long and expensive process of scale-up hinges on scientific feasibility as well as economic concerns. Ideally, the decision to scale up manufacturing will be taken long before efficacy results are available, since scale-up and testing can take several years. Unfortunately, unlike a therapeutic agent, it is very difficult to have a high degree of certainty about preventive efficacy without data from a Phase III trial.

Encouragingly, however, a number of participants noted that HIV "vaccinology" is beginning to become more integrated into the larger world of vaccine research, development and delivery. It is now recognized that progress in overall vaccine development and distribution will undoubtedly help move HIV vaccine development forward, and vice-versa.

Many of the presentations also reflected the need to produce cheap, easily delivered vaccines. These included reports on "edible" vaccines, other simplified delivery systems and new adjuvants that may reduce the dosage or required number of immunizations. The Seattle-based Program for Applied Technology in Health (PATH) presented a plan for making vaccines with improved thermostability available for the developing world.

Francine McCutchan of the Henry M. Jackson Foundation presented interesting data on the molecular epidemiology of HIV epidemics. Using serological methods, Phil Renzullo of the U.S. Walter Reed Army Research Institute of Research (WRAIR) and colleagues demonstrated substantial diversity of HIV strains in infected applicants for U.S. military service. Antibodies preferentially binding V3 loops from A or C, D, or F strains were found in about 2% of applicants and a variant of B that predominates in Brazil was found in another 5%. These atypical B V3 serotypes in the military applicants included a variety of patterns, including B/D, B/F and others, in addition to the "Brazil B" peptide. Researchers also described new recombinant HIV strains in Thailand and China. Interestingly, McCutchan also reported that the progression of HIV diversity was less when HIV was transmitted intravenously through drug use than in a cohort where sexual transmission predominated.

A few preclinical studies of HIV vaccine candidates were presented. The most striking was a late-breaker presentation by researchers at the University of Rochester, the University of Cape Town and MedImmune Corp. Virus-like particles of a strain of human papilloma virus (HPV) associated with cervical cancer were found to be immunogenic when given orally to mice. The virus-like particles can also be modified to act as carriers for other antigens such as HIV.

Data on a number of adjuvant and antigen-presentating strategies were also discussed. Heather Davis of the University of Ottawa presented evidence that in a Phase I hepatitis B trial,

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The View from SmithKline: An Interview with Jean Stephenne

Jean Stephenne is the President of SmithKline Beecham Biologicals. Stephenne began with SB Bio 27 years ago and is largely credited with building the company into the world's largest vaccine manufacturer. With its established malaria vaccine program and growing HIV vaccine effort, SB Bio is well-positioned to play an important role in fighting two of the world's greatest killers. In January 2000, parent company SmithKline Beecham announced that it would merge with Glaxo Wellcome to become the world's largest pharmaceutical company. We spoke with Stephenne at SB Bio's Rixensart, Belgium headquarters.

IAVI Report: How do you see the overall market for vaccines in the world?
Jean Stephenne: It's a market that is growing by 12-15% per year, which is faster than the pharmaceutical market. There are two reasons for this. One, we are putting more new products on the market, which reflects the fact that industry is investing more in research and development. And, two, there is a need for new vaccines, because vaccination is still the only weapon the world has to control many diseases, particularly with the emergence of antibiotic and viral resistance.

How large is the global market for vaccines?
It is about US$3.8 billion for all vaccines.

Given the benefits of vaccination, that's still a pretty small market compared to a single drug like Viagra®, which generates more than US$1 billion alone per year. How do you increase public support for the value of vaccines and vaccine research?
When you are ill, it is easy to ask someone to pay money to buy medicines. But with preventive vaccines, it's very difficult to get a reasonable price for the product. This has been a problem for many years. That's why, in the 1970s, nobody was investing in vaccine development.

There is also a liability problem. Again, going back to the 1970s, as soon as you had a reaction, it was assumed that the vaccine was responsible. And by definition, when you vaccinate millions of children and adults, you will find certain conditions that occur around the time of vaccination.

And since those vaccinated are usually healthy, it is expected that there will never be any side effects, ever. But I have never seen a vaccine - or a drug - that has absolutely no side effects at all. So vaccination is still not highly regarded. But things have improved during the last ten years.

This is the first in a series of interviews with leaders of companies engaged in vaccine development.

Why?
First, there has been better patent protection. Without patent protection, there will be no private sector investment. And there has been a little bit better pricing in Europe, North America and the developing world.

But there is still pressure for industry to supply the world with vaccines at no cost. With 10 million people born in Europe and the U.S. each year, plus 120 million born in developing countries, it will not be easy to supply vaccines to all those who need them. In fact, it will be very difficult.

How do revenues break down in terms of income from North America and Europe compared to the developing countries?
The U.S. and Europe each have about 35-40% of the market. The rest is developing countries.

Are liability concerns still a major problem for vaccine developers?
In the U.S., legislation created in the late 1980s protects industry in terms of liability. But in Europe, such laws don't exist. And we recently saw that this is still an issue, with the erroneous claims that hepatitis B vaccination was associated with multiple sclerosis. So there is still risk of liability here.

The hepatitis B vaccine was first developed in the early 1980s. Today, much of the developing world is still not immunized with this vaccine. What can be done to ensure access to vaccines like this?

The problem is not a question of vaccine availability. It is a lack of funds to procure and distribute the vaccine. If these funds are not made available, I don't see how developing countries will get the vaccine. They cannot afford it. In the wealthy countries you have hepatitis B vaccine that costs less than a bottle of champagne.

It would have to be a good bottle.
Fair enough, a good bottle. But then you go to a developing country, and we're selling this vaccine for one or two dollars per dose. Which is the cost of what? Almost nothing. So on one hand, there is the need for outside funds to procure the vaccine. But even developing countries have to be willing to invest something in health care and vaccines.

I don't think it's a good example to just donate vaccines. There must be co-responsibility. In some countries, the government spends a lot more money on non-health care costs, particularly military expenses. So we need to find new funding mechanisms for vaccines. But every country has to take at least some responsibility for the health of its citizens.

In the wealthy countries like the U.S., insurance companies often do not reimburse adults for the hepatitis B vaccine. But if you get chronic hepatitis B, insurance pays for expensive long-term antiviral therapy. So in many ways, we favor treatment over vaccines.
Yes, you are right. When Mr. Clinton became U.S. President,

there were discussions about vaccines and we defended the need for a profitable industry. Without that, you will destroy investment in vaccine R&D.

The Kerry-Pelosi bill, which was introduced in the U.S. Congress, would provide a tax credit for investment in vaccines. [See article, page 11.] What are your thoughts on this type of incentive?
There must be incentives if industry is to continue investing in vaccines, particularly vaccines for developing countries. Industry has the know-how to develop these vaccines, so you need to give them incentives. The Kerry-Pelosi bill is a good start and we hope the bill passes in this legislative session. But some companies will not benefit from these credits because of their global structure.

Would a vaccine purchase fund be useful?
Absolutely. You have to help industry invest in research and development (known as "Push mechanisms) and also create mechanisms to guarantee the purchase of vaccines ("Pull" mechanisms). If you don't have both, it will not work. With the hepatitis B vaccine, there is a sufficient market in industrialized countries. But with malaria and HIV vaccines, the market in the U.S. and Europe, initially, will not be big enough to justify the research expenses.

Can you give us an overview of SB Bio's vaccine program?
We built this company on the hepatitis franchise - vaccines for Hepatitis A and B. After that, we decided to go with a combination hepatitis vaccine. We are also developing new combination vaccines.

We now believe that the science is far enough along to try to move a candidate HIV vaccine into human trials by the end of the year.

Other areas of research include vaccines for human papilloma virus [some HPV viruses cause cervical cancer] and meningitis. We are already in clinical studies with these and hope to reach the market in the coming years. And we're working on vaccines to prevent chlamydia, CMV and other diseases, but these are more long-term projects.

How is the malaria vaccine program coming?
We've been working in malaria for about seventeen years. Our collaboration with the U.S. Army's Walter Reed Army Institute of Research (WRAIR) has been excellent and has enabled us to continue our research. It is a very complex area but we've generated interesting results in challenge experiments and in clinical trials in Gambia. Does it mean that we have the final vaccine? We have to test that.

What we need now is continued support for the clinical development of this product. We are discussing how to get the support we need to conduct these studies.

And we're considering what to do to ensure supply if the vaccine is effective. We are now at the stage where we must decide whether to invest significant funds in production facilities. This is a critical area where government programs can make a huge difference.

As a company executive who is responsible to shareholders, how do you decide on the level of resources to invest in a malaria vaccine?
I'm responsible for guaranteeing a return on investment to the shareholders. So when you take a program like HIV or malaria vaccine development, it's difficult to decide what to do. If we do not have public help, it will be very difficult.

Our association with Walter Reed is a very good example of collaboration between public and private sectors. We are taking knowledge we have in vaccines and adjuvants and working with WRAIR to try to develop a vaccine.

The HIV vaccine program has more or less the same problem. We have not made a lot of noise about this program, although we have been working on HIV since 1987. Why? Because we needed to establish that it was scientifically feasible to develop a vaccine. And this is not demonstrated by simply moving a product into clinical studies. We needed reasonable pre-clinical data to justify this step.

We now believe that the science is far enough along to begin clinical trials and have a candidate vaccine that we would like to take into the clinic by the end of the year. So, in both malaria and HIV, we have made progress. But we are still a way off.

Is there money to be made from a malaria or HIV vaccine?
It's a very difficult question. If no mechanism is created to purchase the vaccine, I think it will be very, very difficult to build a market. For example, with malaria, we had initially thought there would be a good market for the travel sector from industrialized countries. People could take the shot before they traveled to certain regions. But today we don't believe that a product can meet the challenge. So the market will be in developing countries.

With HIV, I think the first demonstration of efficacy will be in developing countries. And then people will look at whether we can we use it in the Europe and the U.S., where the need is totally different. But traditionally, vaccines do not become available in developing countries until 15-20 years after their introduction. So we all need to act quickly and set up mechanisms for purchasing these vaccines. This will require a major paradigm shift.

What mechanisms do we need to stimulate investment in developing vaccines for developing countries?
First, the public sector needs to continue to fund basic research, as well as clinical development conducted by industry. Second, you need to help fund capital investment, because we'll need to build plants to manufacture the vaccines. You can't make manufacturing decisions too late in the process; otherwise, you will delay availability of the vaccine. This is a critically important issue.

Third, we need a 10-15 year program that provides funds for purchasing the vaccine, so industry is not forced to

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produce the vaccine at no profit. The companies must have a reasonable return. We have to take financial risks, and we will. But if we don't get help, it's going to be very, very difficult.

Gordon Douglas [former president of Merck Vaccines and a member of IAVI's board of directors] has said that the challenges of manufacturing and distributing an AIDS vaccine could be as formidable as developing a vaccine.
Yes. Look at all the existing vaccines that are not available to many people in the world, even where disease is quite severe. And when you have an injectable vaccine, you need an infrastructure to distribute the vaccine. The reason polio control has been so successful is because it's an oral vaccine. Using needles creates significant challenges, including contamination. So distribution mechanisms need to be put in place. These mechanisms exist for some infant immunizations. But with adult vaccination, it is much more difficult, even in industrialized countries.

What made you decide to move your candidate HIV vaccines into human studies?
We are generating some interesting results with different collaborators and have induced some protection in the pre-clinical model. And today, perhaps people are a little more optimistic about an HIV vaccine than they were five years ago. But you still need promising pre-clinical data to justify going into human studies.

How did you start working on vaccines?
I'm an engineer in biology. So vaccines are a good field for two reasons - one, because I find biotechnology fascinating and two, because it gives me the opportunity to work for the health of everyone. There are very few products that provide as much benefit, in terms of protecting people's health, as vaccines.

But it is sometimes very difficult because the benefits of vaccines are not as well-recognized as those of therapeutics. That makes our work more difficult. Developing a vaccine costs as much as developing a drug. But getting a good return on the investment is often much more risky.

If mechanisms to produce and distribute an AIDS vaccine are not put in place, it will be very, very difficult to ensure delivery – particularly since we will need to vaccinate adults.

But companies have also got to do a better job in promoting the benefits of vaccines. You cannot only count on public health organizations to do it.
Yes, I agree. Sometimes we have not done enough.

Let's talk about the merger with Glaxo Wellcome. You have a company that invests more in HIV research than anyone else merging with the world's biggest vaccine companies. Will this help the HIV vaccine program?
There will be scientific synergy and the expertise in the organization will increase. For example, it will be much easier to organize a clinical study of a therapeutic HIV vaccine. And while we have a great deal of expertise in developing vaccines, the merger may give us access to certain technologies. For example, we are investing a lot in DNA vaccines and the merger with Glaxo could help in this area.

Glaxo may also be able to help us design clinical trials in the HIV program. They know a lot about how to design clinical studies for HIV therapies. But in prophylactic vaccine development, we have more experience.

Will your research on one vaccine approach help in developing vaccines for other diseases?
Yes. For example, our malaria vaccine program is helping us develop new adjuvants that may also be useful in other programs. In fact, we are working on an adjuvant that can be tested in both our malaria and HIV programs.

In the past, some people have criticized SB Bio for not doing more in the area of HIV vaccines. How do you feel when you hear this?
These criticisms were voiced two or three years ago. At the time, we said we would invest when the time was right. There is no point investing in a field if you have not studied the basic concept sufficiently.

Ten years ago, there were a number of biotech companies developing HIV vaccines and launching clinical studies. But without solid pre-clinical rationale there is no reason to do these studies.

Our company does not move into human studies without establishing solid pre-clinical data. That is why we were more or less reserved in our activities. Without the necessary scientific information, even testing a product in one thousand people will not move things faster.

Are you optimistic about the prospects for malaria and HIV vaccines?
Our efforts are still in the development stage. But they are worthwhile, because there is a desperate need for these vaccines around the world. We feel good about the work we are doing and are hopeful about being able to help move things forward.

We now believe that the world can have an HIV and a malaria vaccine in 8-10 years. But this will happen only if we work together to support public/private partnerships and put in place new mechanisms to provide real incentives for vaccine development. We have to think very differently than we have in the past. ◆

Uncertain Outlook for U.S. Vaccine Bill

Despite increased support for AIDS vaccines from the White House and Congress, legislative action this year appears unlikely.

by Allison F. Bauer

Notwithstanding growing support from the Clinton Administration and an increasing number of legislators and public health advocates, legislation that includes specific proposals to encourage industry investment in AIDS vaccine development may be stalled for this year.

The "Vaccines for the New Millennium Act of 2000," introduced by Senators John Kerry (Democrat of Massachusetts) and Bill Frist (Republican of Tennessee) and by Representative Nancy Pelosi (Democrat of California), progressed through the 106th Congress, but further progress during this session is uncertain.

A vaccine tax credit is unlikely as long as some companies are lukewarm about it and Congress and the White House are pushing different plans.

Access and other Non-Tax Credit Provisions

The non-tax credit provisions of the bill, including the creation of a Lifesaving Vaccine Purchase Fund and authorization for contributions to the Global Alliance for Vaccines and Immunizations (GAVI) and to IAVI have been incorporated into the "Technical Assistance, Trade Promotion, and Anti-Corruption Act of 2000". This legislation, under the jurisdiction of the Senate Foreign Relations Committee, is a compilation of many smaller internationally focused bills. The entire bill was approved by a voice vote of the committee in late March.

According to reports, Sen. Phil Gramm (Republican of Texas), chairman of the Banking Committee, has placed a "hold" on the bill. The bill was passed out of the Foreign Relations Committee but the Banking Committee, which has jurisdiction over unrelated non-AIDS provisions of the legislation, now wants to hold its own hearings. Notwithstanding the delay on the authorization side, the Senate Foreign Operations Appropriations Subcommittee approved a US$50 million appropriation for the Global Alliance for Vaccines and Immunizations (GAVI) on 10 May. No appropriation was included for either IAVI or the vaccine purchase fund.

R&D Tax Credit Provisions

The tax credit portion of the vaccine legislation, if passed, would provide research and development tax credits for pre-clinical and clinical research and development (R&D) costs for vaccines against AIDS, malaria, and TB, and any other infectious disease that causes over one million deaths annually. As originally introduced, the bill provides a tax credit for R&D costs for these priority vaccines. (The Senate bill provides a 50% credit on *increased* R&D for these vaccines; the House bill would provide 30% credit on *all* qualified R&D on the priority vaccines.) Supporters hoped that the tax credit provisions would be included in the Africa-Caribbean Basin Initiative Trade Bill, but conferees opted not to do so and the compromise bill, without the provisions, was approved by both the House and Senate.

According to one legislative staff member, the tax credit failed to become part of the Africa bill for a number of reasons. Industry was not actively working to support and secure the tax credit, with only two companies, American Home Products (the parent company of Wyeth Lederle Vaccines) and SmithKline Beecham Biologicals, vigorously pushing for its inclusion. "It is nearly impossible to give a tax credit to industry when the companies are lukewarm about getting it," said the staffer. And, in the view of this influential legislative aide, the Clinton Administration could have been more helpful. "They were supporting one version of the credit while key congressional staff was pushing for another. If a tax credit is going to be passed, the groups advocating for it need to be working together rather than on opposing sides." It is unclear whether there will be other opportunities to include the R&D tax credits on alternative legislation this year.

Compulsory Licensing and Parallel Importing Provisions

A provision sponsored by Senators Dianne Feinstein (Democrat of California) and Russ Feingold (Democrat of Wisconsin) that would have guaranteed access to inexpensive generic AIDS drugs for African countries was also excluded from the Africa-Caribbean Basin Initiative trade bill. This amendment called for relaxing intellectual property standards to allow countries to import or manufacture cheaper versions of anti-AIDS drugs patented by U.S. pharmaceutical companies. The companies opposed this language, warning that it would set a dangerous precedent. They argued that the availability of drugs in Africa has less to do with pricing and more about the lack of infrastructure to deliver the drugs and the failure of some African governments to develop comprehensive AIDS programs.

Tempers flared in the House chambers as police detained protestors from ACT-UP after they twice interrupted a vote on the Africa-Caribbean Basin Initiative trade bill on 4 May.

After the trade bill passed the House easily, Sen. Feinstein urged the White House to issue an executive order to carry out

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delivered by the Salmonella was developed by Oxford University's Andrew McMichael as part of IAVI's first partnership. (See *IAVI Report,* January-March 1999.)

Unlike most viral vectors, bacteria can hold large amounts of foreign DNA, are highly stable, and are simple and inexpensive to manufacture. This bacterium also offers the potential to deliver vaccines orally or intranasally. Because it is orally administered, the new vaccine is expected to elicit mucosal immune responses, which are thought to be the first line of defense against sexually transmitted HIV.

"This vaccine approach stresses ease of use and low cost, which are key factors for reaching people in developing countries," said Seth Berkley, president of IAVI. Berkley also noted that, like IAVI's three previous VDPs, the new agreement includes legal guarantees to help ensure that any successful vaccine will be distributed in developing countries for a reasonable price. The simple manufacturing process, he added, could also eventually allow this vaccine to be produced in developing countries.

Gallo, the co-discoverer of HIV, noted that "this new bacterial vector induces responses not only to microbes but to certain cancers as well. IAVI's fast-track philosophy and technical assistance will help speed this approach into human tests."

Uganda was the first country in Africa to host an AIDS vaccine trial. According to Francis Omaswa, the country's director-general of health services, "Our new partnership with IAVI will help ensure that we maintain our leadership in this area, doing whatever we can to accelerate the development and testing of AIDS vaccines appropriate for use in Africa."

The Salmonella-DNA vaccine, says Wayne Koff, IAVI's vice president for research and development, "links two independent vaccine strategies (orally administered recombinant Salmonella vectors and DNA vaccines) with the goal of improving upon both."

Koff noted that using the HIV DNA vaccine developed by the Oxford-Nairobi partnership "will enable us to move this new product into clinical trials faster, and compare it directly with the Oxford group's injectable DNA vaccine. Head-to-head comparisons of candidate vaccines in Phase I trials is an integral component of our overall program."

The new Salmonella-DNA vaccine approach is the result of intensive basic research on the delivery of HIV vaccines by bacterial vectors, carried out by George Lewis, director of the IHV Division of Vaccine Research, and fellow researcher David Hone.

The DNA vaccine encodes pieces of HIV *gag* and polyepitopes. According to Lewis, studies in mice show that a Salmonella vector carrying foreign DNA generated significantly greater CTL responses than the same vector expressing the foreign proteins.

The Salmonella vector developed by the IHV researchers has already been tested in 37 people in a Phase I trial funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID). That vector, which is engineered to express HIV envelope proteins, has reportedly shown limited immune responses. Researchers are now evaluating whether higher doses of the vector will generate better responses. NIAID is also supporting development of Salmonella to deliver DNA which encodes a novel envelope antigen.

The disappointing immune responses seen with the lower doses could be the result of "over-attenuating" the vector, making it so weak that it is no longer immunogenic enough. IHV researchers say they are waiting for results from the higher doses before making any final conclusions about the vector's immunogenecity. They also note that because the trial was the first-ever human study of an HIV bacterial vector, they had to make sure it was safe and did not induce Salmonella disease (i.e., diarrhea) in participants.

If that strain of Salmonella is determined to be sufficiently immunogenic, human trials of the Salmonella-DNA vector could begin within 18 months, according to Lewis. The research team is also looking at a range of other attenuated Salmonella strains that could be used.

Anthony Fauci, director of NIAID, told a reporter that the vaccine is "theoretically the right approach." However, he cautioned that "we've been fooled so many times about new vaccines that I've hesitated to talk about this one until now, but I really like it." ◆

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her HIV/AIDS initiative. She did not have to wait long for President Clinton to act: he signed an Executive Order on 10 May that for the first time allows developing countries to import and manufacture cheaper version's of the world's most effective AIDS drugs without fear of punishment from U.S. trade authorities. The following day the Senate, too, easily passed the trade bill.

European Proposals Being Considered

The European Commission is also examining the possibility of using tax credits to spur private sector investment in AIDS vaccines. But observers believe that such credits are more likely to be part of a broader plan designed to stimulate vaccine development, which will be proposed by the European Commission to Parliament and Council in the coming months. In terms of tax credits for vaccine development, one key question still needing clarification is whether such programs can be instituted, given European investment and competition. ◆

Allison Bauer is the policy director of the Washington, DC-based AIDS Vaccine Advocacy Coalition.

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CpG-containing oligodeoxynucleotides were safe and could provide immune stimulation.

Clinical trials of a number of candidate HIV vaccines were also described. A Phase I/II trial of VaxGen's B/E bivalent gp120 vaccine showed the expected profile of safety and immunogenicity as measured by antibodies and neutralization of MN strains of HIV. In a WRAIR study, Aventis Pasteur's oligomeric envelope protein (o-gp140) tested alone and in combination with ALVAC-HIV (vCP205) was safe and showed some evidence of neutralization against a primary strain of HIV. The o-gp140 construct was formulated with a novel adjuvant known as PCPP.

The meeting featured at least two talks on overall vaccine safety issues. Frederick Miller of the U.S. Food and Drug Administration (FDA) described collaboration between FDA and the American College of Rheumatology that will define criteria for evaluating possible induction of autoimmunity by vaccination and guide how such reports should be investigated. This effort could bring some much-needed critical scientific data to bear on a controversial topic. In addition, John Petricciani, vice president of the International Association for Biological Standardization in Geneva, reviewed progress toward relaxing limits on the use of a broader variety of tissue cultured cells to produce vaccines. Uncertainty about which cells may ultimately be acceptable could be a stumbling block to development of particular vaccine approaches. ◆

Pat Fast is associate director of clinical research at Aviron, a California-based biotechnology company, and the former associate director of the Vaccine and Prevention Program at the U.S. National Institute of Allergy and Infectious Diseases' Division of AIDS.

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directed mostly at conformational epitopes. Pilot studies using a prime-boost regimen in monkeys are now underway, together with Leo Stamatatos of the Aaron Diamond AIDS Research Center. So far, V2-deleted oligomers (a more immunogenic form of gp140), but not gp120 monomers, have induced antibodies that neutralize some primary isolates (including the standardized panel provided by NIAID).

Giuseppe Scala of NIAID described a very different approach to developing new antigens, based on screening large libraries of random peptides displayed on the surfaces of bacterial viruses (bacteriophages). The strategy was to select those phages recognized by antisera from HIV-infected people, which presumably contain peptides that mimic the conformation of an authentic HIV epitope. In this way the researchers identified five "mimotopes" (antigenic mimics) recognized by neutralizing antisera to HIV-subtype B; these also bound to antisera against subtypes A, C, D, E and F. As antigens, the mimotopes induced epitope-specific neutralizing antibodies in mice. Studies of their immunogenicity in monkeys are now in progress.

Natural Resistance to SIV in Mamu-A*01 Monkeys

Genoveffa Franchini (NCI, Bethesda) presented a surprising result from a study of SIV vaccines in a 70-monkey study: animals carrying the Mamu-A*01 histocompatibility allele [belonging to a family of genes that regulates immune responses] appear to have some natural resistance to SIV. This finding emerged from an experiment designed to test a canarypox-SIV vaccine with and without monomeric gp120 boost, where even unvaccinated Mamu-A*01 monkeys (but not animals with other alleles) were able to control viremia after challenge. They also had less CD4+ cell loss and a delayed disease progression relative to macaques with other alleles. This ability to control viral load is associated with the presence of CD8+ T-cells that recognize *gag*, *env* and *tat*, especially in lymphoid tissue associated with the gastro-intestinal tract. "If canarypox vaccine studies had been done only in Mamu-A*01 animals, any reasonable researcher would conclude that the vaccine had no activity at all," said Franchini. To avoid such misleading results, she emphasized that experimental vaccines should be tested in a group of animals that is heterogeneous with respect to the histocompatibility alleles.

Although eliminating the Mamu-A*01 animals reduced the trial's statistical power, Francini could still show that although canarypox-SIV did not protect against infection (since nearly all animals became infected after challenge), it did decrease viral load, protect against CD4+ cell loss and increase overall survival. In terms of CTL responses, 20% of the vaccinated animals had CTLs against *gag* or *env* at all 3 times measured; 50% were positive twice and 70% once. Animals receiving the gp120 boost developed neutralizing antibodies to the homologous lab strain of SIV but not against heterologous viruses.

Other HIV Vaccine Candidates in Animals

Although inactivation of whole viruses is a classical strategy used to make many licensed vaccines, there has been relatively little work (or optimism) on this approach for HIV. One of the few efforts is that of Larry Arthur and collaborators (Frederick Cancer Research Center, Maryland), who developed a method for chemically inactivating HIV or SIV that preserves the virions and their immunogenicity apparently intact. Under development for several years, Arthur presented results from a small study of whole killed SIV vaccines, which showed that 5/6 macaques were protected against the homologous strain of SIV, but that the vaccine did not protect against heterologous strains. Since the heterologous strain used in the latter experiments was low in surface gp120 (a

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Vaccines at Durban

Date / Time/Topic	Venue

Sunday–Friday, 9–14 July, 2000

IAVI-SAAVI Booths
- I.C.C. Main Exhibition Hall (donated by Serono International SA, Geneva)
- NGO Village Exhibition Booths (Booth No. 23)

Sunday, 9 July, 2000

17:00 ***Press Briefing*** Ensuring Global Access to HIV Vaccines (Press only)	Press Conf. 1 I.C.C. Ground Level

Monday, 10 July, 2000

13:00–14:30 Debate: Track C Vaccine Preparedness	City Hall 13
14:45–16:15 ***IAVI-sponsored Roundtable*** HIV Vaccines for Developing Countries: Development, Access and Delivery	I.C.C. 5
15:00–18:00 ***ICASO-UNAIDS-IAVI-sponsored Roundtable*** Vaccine Skills Building	C-Hall 5: A. Luthuli Side Hall
16:30–18:00 **Debate: Vaccines for Testing in Developing Countries Should be Matched to the Dominant Local HIV Strain/Subtype**	I.C.C. 1

Tuesday, 11 July, 2000

13:00 ***Press Briefing*** IAVI's Scientific Program for Development of an HIV Vaccine (Press only)	Press Conf. 1 I.C.C. Ground Level
13:00–14:30 Debate: Track A New Vaccine Designs I	Playhouse 12
14:45–16:15 *IAVI-SAAVI Roundtable* AIDS Vaccine Development for Africa	City Hall 13

Tuesday, 11 July, 2000 (cont.)

18:30–20:30 *IAVI-ICASO-UNAIDS Satellite Symposium* Understanding HIV Vaccine Development: A Community Discussion Light refreshments to be served	I.C.C. 4

Wednesday, 12 July, 2000

13:00–14:30 **Session** New Vaccine Designs	Playhouse 12
14:45–16:15 **Session** HIV Vaccine Trials	Royal 14
16:30–18:00 Session CD8/CD4 cells: Implication for Vaccine Development	Playhouse 11
16:30–18:00 **Debate: Track C** Therapeutic Vaccine is Useful Strategy for HIV Therapy	I.C.C. 1

Thursday, 13 July, 2000

9:00–11:00 **Plenary 5: Challenges of HIV Vaccine Development**	I.C.C. 1
11:30–13:00 ***ICASO-UNAIDS-IAVI-sponsored Community Mamelang Session*** HIV/AIDS Vaccines and the Work for Communities in Africa	City Hall 13
13:00–14:30 **Joint Track Symposia** HIV Vaccine Trials: Ethics	I.C.C. 4
13:00–14:30 **Session** Recruitment for HIV Vaccine Trials	D.E.C. 7

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major target antigen of the vaccine), the researchers are repeating the work using a strain with more gp120. The protected animals did not show sterilizing immunity but initially had viremia, which was then cleared (similar to measles and polio vaccines).

Stephen Dunham of the University of Glasgow reported on efforts to develop DNA vaccines against FIV, and to test whether cytokine adjuvants impact their efficacy. The researchers set out to improve on an earlier DNA vaccine that protected against the homologous FIV strain but not against more pathogenic, heterologous strains. This time they used a DNA defective in integrase (but with an intact reverse transcriptase gene, permitting one round of replication after vaccination) administered with either IL-12 or IL-18 as an adjuvant. The trial showed that, although either cytokine could lead to stronger CTL responses, they did not improve the level or breadth of protection. The next step is to test their DNA in a prime boost combination.

Ethics of AIDS vaccine trials

This session featured interesting talks from two developing country researchers involved in conducting or planning HIV vaccine trials in their respective countries.

Omu Anzala of the University of Nairobi spoke about a Phase I trial of a DNA/MVA vaccine, based on a Kenyan isolate of HIV subtype A, that is set to begin later this year. Although it will enroll only about 40 low-risk volunteers, mostly from the university community, the proposed trial has garnered tremendous media attention and spurred national discussion. According to Anzala, the trial has been received very positively, largely because of its genesis: the Nairobi team has conducted research on exposed, seronegtive sex workers in this city since 1988, work that formed the basis for developing this candidate vaccine through a collaboration with researchers from Oxford University and the University of Manitoba. "It's been very important that this is a partnership, not just researchers coming to test a finished vaccine," Anzala said.

He also described the questions being raised in the country, most of which revolve around informed consent. While confidentiality is a key principle, there has also been much discussion of the role of trial participants' family members, especially spouses and parents of those just over the legal age of consent. Who is informed about the participation, especially if pre-trial screening shows a volunteer to be HIV-positive? Other issues under discussion include invasion of privacy concerns over questions used to assess a person's level of risk (including number of sex partners) and their other risk-related behaviors, as well as HIV treatment for participants who become infected while in the trial.

Next, Sricharoen Migasena of the Taksin Hospital in Bangkok spoke about the ongoing VaxGen trial in Thailand, the only Phase III HIV vaccine trial launched in the developing world, and described why the country decided to approve the trial. Because Thailand has conducted many clinical trials in the past, it has an established system for ethical and scientific review that goes back more than two decades and encompasses a National Ethics Committee and many institutional review boards. When the AIDS epidemic took off in the mid-1980's, Thailand became active in running Phase I and Phase II HIV vaccine trials (10 so far), in the process establishing additional infrastructure for laboratory work and prevention counselling. The decision to move ahead with the VaxGen Phase III trial was based on several considerations, including scientific merit (could the trial yield valuable information?), a risk-benefit analysis and the available infrastructure. Participants who became infected during the trial will receive treatment according to the national standard, which at present is two drugs (AZT and ddI or 3TC). Migasena said that the decision not to offer triple therapy (unless this becomes the national practice) was made out of concern that a higher standard of treatment would constitute a form of inducement for (high-risk) people to participate in the trial. ◆

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.

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.

IAVI at Durban

The upcoming XIII International AIDS Conference, to be held on 9 July–14 July 2000 in Durban, South Africa, will feature a wide-range of scheduled sessions, symposia and discussions on HIV vaccines. IAVI is also sponsoring a number of different symposia, roundtables and press briefings. IAVI-sponsored programs at the conference are listed below. A comprehensive listing of vaccine-related events is on page 14.

IAVI-SAAVI Booths

9–14 July

- I.C.C. Main Exhibition Hall (*donated by Serono International SA, Geneva*)
- NGO Village Exhibition Booths (Booth No. 23)

Press Briefing

Ensuring Global Access to HIV Vaccines

Sunday, 9 July, 17:00
Press Conference 1 – I.C.C. Ground Level
(Press only)

Press Briefing

IAVI's Scientific Program for Development of an HIV Vaccine

Tuesday, 11 July, 13:00
Press Conference 1 – I.C.C. Ground Level
(Press only)

IAVI-sponsored Roundtable

HIV Vaccines for Developing Countries: Development, Access and Delivery

Monday, 10 July, 14:45 to 16:15
I.C.C. 5
Speakers: Mandeep Dhaliwal (Chair), Geeta Rao Gupta (Co-Chair), Lieve Fransen, Seth Berkley, Jacques-François Martin, J. Mehta, Helen Rees, Martha Ainsworth

ICASO-UNAIDS-IAVI Session

Vaccine Skills Building

Monday, 10 July, 15:00 to 18:00
City Hall 5, A. Luthuli Side Hall

IAVI-SAAVI Roundtable

AIDS Vaccine Development for Africa

Tuesday, 11 July, 14:45 to 16:15
City Hall 13
Speakers: Crispus Kiyonga (Chair), Walter Prozesky (Co-Chair), William Makgoba, Carolyn Williamson, Dorothy Mbori Ngacha, Omu Anzala, Peter Mugyeny, Sophia Mukasa Monico, Wayne Koff

IAVI-ICASO-UNAIDS Satellite Symposium

Understanding HIV Vaccine Development: A Community Discussion

Tuesday, 11 July, 18:30 to 20:30
I.C.C. 4
Moderators: Moustapha Gueye (Senegal), David Gold (U.S.A.); *Speakers:* Seth Berkley (U.S.A.), Jose Esparza (Switzerland), Richard Burzynski (Canada), Sophia Mukasa Monico (Uganda), Rubaramira Ruranga (Uganda), Ronaldo Mussauer de Lima (Brazil), Sricharoen Migasena (Thailand), Dean Khumalo (South Africa), Sam Avrett (U.S.A.), Ruth Nduati (Kenya), Peter van Rooijen (The Netherlands)

Light refreshments to be served

ICASO-UNAIDS-IAVI Community Mamelang Session

HIV/AIDS Vaccines and the Work for Communities in Africa

Thursday, 13 July, 11:30 to 13:00
City Hall 13

www.iavi.org

IAVI's updated website debuts for the conference. Visit **www.iavi.org** for news and information about AIDS vaccines and to subscribe to the *IAVI Report*.