

Warming Trends at Keystone Vaccine Conference

Talks highlight human trials, T-cell markers and antibody approaches

BY EMILY BASS AND RICHARD JEFFERYS

Unseasonably high temperatures and record-low amounts of snow set the backdrop for this year's Keystone Symposium on "HIV Protection and Control by Vaccination" in the Colorado Rockies. Inside, the thaw was more welcome, as early clinical trials data started to flow through the vaccine development pipeline. In the corridors, participants noted the welcome move towards convergence of virology and immunology, with virologists looking increasingly at approaches for immune control of HIV and immunologists envisioning therapeutic uses for vaccines alongside the goal of preventing disease and ultimately, infection.

KEYNOTE CONCEPTS

Two keynote speakers addressed some of the challenges faced by HIV vaccine developers specifically tackling either the cellular or humoral arm of the immune system.

Cellular immunologist Rafi Ahmed (Emory University) focused on a subset of T-cells responsible for immunological memory, which enables the immune system to "remember" microbes or vaccine antigens encountered long ago and to respond quickly if and when (re-)infection occurs. After reminding the audience that he works not on HIV but on viral infection in mice, Ahmed plunged into

continued on 2 ▶

EXPANDED DNA-MVA PRIME-BOOST TRIAL BEGINS IN UK

On April 4, 2002, UK researchers immunized the first volunteer in a Phase IIa trial of an HIV-DNA vaccine and a second vaccine based on MVA (MVA.HIV) a weakened version of vaccinia virus. The study, headed by Jonathan Weber of London's Imperial College of Science, Technology and Medicine, is taking place there and at Oxford University, and will enroll 120 volunteers. It is sponsored by IAVI and the UK Medical Research Council.

Both vaccines contain most of the HIV-*gag* gene derived from subtype A, the most common subtype in Kenya, fused to a string of 25 partially overlapping CTL epitopes from *gag*, *pol*, *nef* and *env*.

They were developed by

Oxford researchers Tomas Hanke and Andrew McMichael in partnership with scientists at the University of Nairobi. Data from a small Phase I prime-boost trial, presented at the recent Keystone Symposium (see above), showed cellular immune responses against HIV in all vaccinated participants.

The new expanded, double-blinded trial is being called a Phase IIa study by the Oxford team. Sometimes referred to as a Phase I/II, such intermediate-size trials typically enroll a larger number of volunteers than Phase I safety studies and gather information on optimal vaccine dosing and immunization schedule, but do not enroll people at high risk for HIV infection. Participants in

the UK trial will receive one of two DNA doses or a placebo, followed by MVA.HIV or placebo. They will also be randomized into two further groups to test different intervals between prime and boost.

The DNA and MVA.HIV vaccines first entered human studies in August 2000 and have been tested in 26 healthy, HIV-negative volunteers in the UK. Clinical trials are also underway in Kenya through the Kenyan AIDS Vaccine Initiative (KAVI) and the University of Nairobi. The Kenyan team has completed a Phase I HIV-DNA study and enrolled 12/18 individuals in an MVA.HIV trial. Upon completion of the latter, KAVI will launch the first of a series of prime-boost trials. —EB

Inside:

African AIDS Vaccine Programme Arrives on the Global Stage 3

World Economic Forum Discusses Global AIDS Vaccine Delivery 5

IAVI Announces Vaccine Partnership with Swedish Company 6

France's AIDS Vaccine Program: An Interview with Michel Kazatchkine 7

Licensing an AIDS Vaccine in Developing Countries: An Interview with Julie Milstien 10

AIDS Vaccine Symposium at Barcelona 12

Vaccine Briefs 16

his team's extensive studies on the generation, maintenance and function of CD8 memory cells and on what these findings imply for designing more effective immunization regimens.

Using sophisticated microarray technology, he showed that the process of generating antigen-specific memory cells from "naïve" precursors involves changes in the expression of thousands of genes, extending over several weeks—suggesting that prime-boost immunization schedules should plan enough time between prime and boost for this full maturation of memory cells. Zeroing in on one specific molecular change, Ahmed identified a cell surface protein called CD62L (or L-selectin) that could be a marker for resting ("central") memory cells. CD8 T-cells appear to lose and reacquire CD62L as they transition from naïve to central memory T-cells, and reacquisition is correlated with the ability to mount a robust proliferative response to viral infection.

Ahmed then examined how antigen dose affected both the initial number of antigen-specific CD8 T-cells ("burst size") and the eventual number of CD62L-expressing central memory cells. The larger the initial burst, he said, the larger the eventual memory cell pool—but the longer it took them to emerge. Drawing a message for vaccine developers, this suggests that the interval between prime and boost immunizations should increase relative to the strength of the prime.

Ahmed also reviewed data showing that antigen is not required to maintain memory CD8 T-cells and described his group's search for factors other than antigen that might play a role. One of his lead candidates is the cytokine IL-15, based partly on studies of "knockout mice" that lack the IL-15 gene; these animals showed a gradual attrition of their memory CD8 T-cell pool, apparently stemming from a drop in proliferation rate. Later in the meeting, Ahmed's Emory colleague Françoise Villinger presented a poster supporting the notion that IL-15 might be a useful adjunct to vaccination: 4 macaques immunized against influenza and then given a short course of IL-15 had 4-5 fold more flu-specific memory T-cell than animals receiving vaccine only, and the elevated levels have so far persisted out to six months follow-up. In contrast, IL-2 given to 4 animals led to only transient increase in memory T-cell numbers.

Next, Joseph Sodroski (Dana Farber Cancer Institute, Boston) turned to the problem of inducing broad neutralizing antibodies (NABs) to primary HIV strains, which no vaccine has yet achieved, reviewing the obstacles and outlining one new approach he is pursuing. He and collaborator Rich Wyatt (Vaccine Research Center [VRC], Bethesda) found that the binding of HIV's gp120 envelope protein to CD4, one of two cell surface receptors for HIV, requires an atypically large expenditure of "ordering energy" to rigidify gp120's flexible structure. Likewise, antibody binding to neutralizing epitopes in gp120, usually concealed within the molecule's interior, is also ener-

getically unfavorable. To overcome this obstacle, Sodroski and Wyatt are exploring "molecular plugs" for a 10-angstrom-deep cavity in the gp120 structure that is a pivot point of floppiness. Here, the goal is to stabilize gp120 in a conformation that exposes usually-concealed NAB epitopes, thereby allowing easier NAB induction.

HUMAN TRIALS DATA

Merck's Adenovirus-based Vaccines

Emilio Emini, director of Merck's vaccine division, opened the session on clinical trials with updated data on its adenovirus-based vaccine, a proof-of-concept construct containing HIV-*gag* in an Ad5 vector. Reporting on the highest-dose group (10^{11} viral particles) in a Phase I dose-response study presented at the recent Retrovirus conference (*IAVI Report*, Jan/Feb 2002, p.1), Emini said that after the first two injections 7/9 volunteers showed CD8 T-cell responses.

(Responses were measured by ELISPOT assays using interferon (IFN)-gamma, which is secreted by activated T-cells.) This was the highest proportion of responders seen with Ad5-*gag* in any dosage group so far, although coincidentally this group had fewer volunteers with pre-existing adenovirus immunity (defined by Merck as NAB titers above 1:200) than the next-lowest dose group (10^7). This random distribution of people above Merck's threshold makes it difficult to draw conclusions for now about dose response in the context of pre-existing immunity.

Emini also presented data using much lower doses of Ad5-*gag*, in this case as a boost for a DNA-*gag* vaccine. Macaques boosted with 10^7 Ad5-*gag* particles after a DNA-*gag* prime responded as strongly or better than those given 10^6 particles without a prime, depending on NAB levels.

In addition to these trials, Merck has started a prime-boost study of DNA-*gag* plus Ad5-*gag*, along with several trials in HIV-infected people, looking towards possible therapeutic use. For preventive vaccines, plans are underway to begin a much larger Phase I study.

Oxford-IAVI Prime-Boost Trials

Oxford University's Andrew McMichael followed with preliminary results from trials of DNA and MVA-based vaccines (DNA-HIVA and MVA.HIV) in the UK, sponsored by Britain's Medical Research Council and IAVI. He began by reviewing the separate DNA and MVA studies, which detected T-cell responses to HIV in the majority of volunteers (based on ELISPOT assays using IFN-gamma). Responses to the DNA-HIVA vaccine (100 or 500 µg given at days 0 and 21) were mostly low, and were dose-independent; a few came up only months after the final immunization. MVA.HIV vaccinees showed peak immune responses 21 days after the second of two immunizations with 5×10^7 plaque-forming units. Responses to DNA-HIVA were a mixture of CD8 and CD4 T-cells, while MVA.HIV responses were predominantly CD8 T-cells.

“The optimal interval between prime and boost immunizations may increase with the strength of the prime.”

continued on 13 ▶

African AIDS Vaccine Programme Arrives on the Global Stage

BY EMILY BASS

On June 3-4, scientists, policy-makers, global health experts and other participants in the vaccine trials arena will gather in Cape Town, South Africa, for an international forum on the African AIDS Vaccine Programme (AAVP). The meeting will be an expanded debut for the AAVP, which has maintained a low profile since its inception in 2000. Planners hope that the gathering, which is co-sponsored by many international stakeholders in vaccines, will take the program to the global stage, with substantially expanded funding and political buy-in to support AAVP.

It's a timely move. Trials and preparations are percolating at many African sites, notably in Uganda and Kenya, which have already garnered some Phase I trial experience, and South Africa, which is now considering its first protocols. And even as scientists and communities navigate the regulatory, ethical and media mazes surrounding these small studies, they're sizing up bigger challenges: preparing for large-scale trials and eventual delivery of a licensed vaccine.

As plans for scale-up proceed, African scientists are looking to supplement the bilateral international partnerships which already abound on the continent. "In the past we [African vaccine researchers] have worked in isolation from each other," says Pontiano Kaleebu, principal investigator at the Uganda Virus Research Institute and a member of the AAVP Biomedical Sciences committee. "This must begin to change."

This move towards pan-African collaboration brings challenges: Is consensus across

borders needed on issues like ethics guidelines, standards of treatment and care in vaccine trials, or strategies for testing vaccines against different HIV subtypes? Where can individual countries and stakeholders afford to go their own ways? How will AAVP leaders who already collaborate with international partners balance continent-wide goals with partnership-driven concerns? And how can countries which do not host trials—but have serious epidemics and therefore a stake in finding a vaccine—contribute to the overall effort?

As AAVP attempts to grapple with these issues on a continental scale, it has set itself the tall task of involving every country, spanning the broad spectrum of capacity, stability and wealth that defines Africa today. "The principle of AAVP is that every African country should be involved [in AIDS vaccines]," says José Esparza, head of the WHO/UNAIDS HIV Vaccine Initiative, which helped launch the AAVP in 2000 and provided US\$ 1 million in start-up funds. "We should not encourage every country to do vaccine trials. But vaccine preparedness? Yes."

AAVP began with research and education: creating inventories of existing ethics documents, organizing workshops for researchers to discuss good clinical practices or learn key laboratory techniques, and collating information on the preparation of national vaccine plans. This set of activities has helped AAVP get its feet wet for the hybrid role it hopes to play as participant-advocate-advisor—not funding trials or stocking the pipeline, but helping to build infrastructure and representing African scientists

in discussions of these efforts.

To this end, the Programme is prioritizing capacity-building for trials, and training researchers and clinicians—activities that will supplement work already being done. "AAVP is not going to reinvent the wheel," says Malegapuru William Makgoba, chair of the AAVP steering committee and head of South Africa's Medical Research Council (MRC). "It will spin the wheel that is already rotating. We need to accelerate and support efforts already coming from different parts of the world."

To play this role, AAVP needs to build strong relationships with the world's vaccine stakeholders. That's where the June meeting will be crucial: AAVP will present its progress so far and its future agenda, and then spell out the resources needed to achieve it. The draft plan calls for US\$ 5-6 million a year for AAVP core activities. Adding in funds to catalyze African vaccine work on a larger scale—including preparedness activities, clinical trials site development and staff training—the total comes to roughly US\$ 230 million over the next seven years, according to Esparza. And he stresses that AAVP need not receive these funds directly: much of it could go through existing bilateral partnerships that can help AAVP meet its strategic milestones.

"We will do what is not being done by others," says Kaleebu. "We can share national vaccine plans and trial plans with countries that want to get involved. That will help a lot. But we still need money."

AAVP's move to become a catalytic force in Africa takes

continued on 4 ▶

place against a dynamic backdrop in which AIDS is receiving increasing attention as a development issue (see article, page 5), and new mechanisms like the Global Fund to Fight AIDS, Tuberculosis and Malaria are funneling money into developing countries.

Whether or not the AAVP succeeds with this and the other considerable challenges it faces, scientists say that it has already set an important precedent. "Africans have never had this kind of forum," says Makgoba. "The only time we learned what was happening was when we met in Geneva or in Japan. We never met amongst ourselves in Africa to say, 'These are our priorities. These are the challenges we face. If you want to help us, help us this way.'"

Filling a Need

AAVP was born in Nairobi, Kenya at a meeting in June 2000, shortly before the 13th International AIDS Conference in Durban. At that first meeting, Africa's leading AIDS vaccine researchers signed the "Nairobi Declaration," which called on African leaders to make AIDS vaccine development a top priority, laid out a timeline and framework for activities, and increased public education and political lobbying on the importance of vaccines.

Until now, AAVP has focused on laying a foundation for its global efforts through behind-the-scenes activities, and has not yet sought a vocal role in African advocacy. "We, as stakeholders, have not come out together explicitly for AAVP [as the] voice for Africa," notes William Makgoba, senior specialist of the Botswana-Harvard Partnership and the Princess Marina Hospital, an expansion site in the US-sponsored HIV Vaccine Trials Network (HVTN).

But much has happened in the past two years, with an

array of international research teams and African partners now conducting or preparing for vaccine trials. In this context, many on the continent are looking to groups such as AAVP to articulate a widespread concern that in-country efforts should spill over to the continent as a whole. "We don't want a situation where, simply because the population participating in the research was in Botswana or Uganda, they are the sole beneficiaries," says Makgoba.

Laying Out an Ambitious Plan

At the June meeting, AAVP will present the work plan of its steering committee and five working groups: Advocacy and Resource Mobilization; Biomedical Sciences; Population-Based Studies; Ethics, Law and Human Rights; and National Strategic Planning.

In 2001-2002, just under half the AAVP budget went to the Biomedical Sciences group, which aims to identify areas for research collaborations and help build capacity for regional reference centers which can characterize HIV isolates and immune responses. That, in turn, is based on a now-completed inventory of labs and trained personnel, and on the ongoing program of lab training courses co-sponsored by WHO/UNAIDS.

After Biomedical Sciences, the Ethics, Law and Human Rights (ELH) group is farthest along in its activities, says Esparza. This group, which works closely with the ethics committee of the South African AIDS Vaccine Initiative (SAAVI), has conducted an inventory of ethics resources (such as guidelines for clinical research) in African countries, which it is collecting into a central clearinghouse. The results of a "Symposium and Networking Forum on Ethics, Law and Human Rights" held in Durban

at the end of April will be presented at the Cape Town meeting in June.

The remaining AAVP groups are still laying out their agendas. Population-Based Studies hopes to serve as a match-maker between groups developing vaccine candidates and those working with local populations. The National Strategic Planning Committee will support country efforts to develop national AIDS vaccine plans, and the Advocacy group will focus on fundraising and media outreach.

So far, AAVP has collated the information gathered in these different groups into "country profiles" that outline the capacity, readiness and epidemiology of AIDS in different countries. The hope is that such information will help donor countries and research institutions make educated choices about how to get involved.

Building Capacity, Expanding Training

AAVP's roster of members is a Who's Who of African AIDS researchers. But as robust as this group is, its members are quick to point out that one of the most serious challenges their countries face in doing research or preparedness work is the serious shortfall in trained personnel—stemming from poor resources and infrastructure for training and from the political instability and lack of opportunity that drives trained young people to work abroad.

Last November, this plight was presented in stark relief during a talk in Botswana at a Harvard AIDS Institute "think tank" meeting on developing vaccine trials networks in Africa. Zimbabwean scientist Stephen Chandiwana, director of the Blair Research Institute in Harare, showed a slide of a solar eclipse, with the sun gone dark. Standing before this

continued on 6 ▶

WORLD ECONOMIC FORUM DISCUSSES GLOBAL AIDS VACCINE DELIVERY

BY EMILY BASS

It is 2007 and NewVaxCo, a hypothetical company, has just announced that its HIV vaccine proved highly effective in Phase III trials. The road to this great success has been bumpy: NewVaxCo spent grants and internal funds to develop the vaccine, and lost money along the way. In anticipation of public demand, it transferred intellectual property rights for the vaccine to four large developing countries—and is now worried about recouping its losses. More hurdles loom, including the time-consuming process of applying for separate licenses in countries around the world. And even though a tiered pricing scheme that charges poor countries much less than wealthy ones is in place, it still leaves the vaccine out of reach for many. What should NewVaxCo—and the world—do?

This scenario was the starting point for a workshop, entitled “Delivering an AIDS Vaccine,” attended by nearly 100 participants at the World Economic Forum (31 Jan - 5 Feb 2002). The session was the only disease-specific event at the five-day meeting that brought the well-known annual gathering of world leaders from its usual home in Davos, Switzerland to New York. (A well-attended discussion on global public health took place two days earlier). A background document, “Delivering an AIDS Vaccine: A Briefing Paper” (www.iavi.org/pdf/wef2002.pdf), prepared by IAVI in cooperation with the WEF, was distributed on the Internet and at the workshop.

The session began with IAVI President Seth Berkley introducing the scenario, placing it in a broader context by noting that “an AIDS vaccine is not the only International Public Good we need. We need female-controlled microbicides, simpler diagnostics, better drugs. The principles discussed here can be used for these other public good approaches, as well as to help develop new tools for malaria, TB and other diseases of poverty.”

In addition to Berkley, discussion leaders included Gro Harlem Brundtland, (Director-General of the World Health Organization (WHO), Peter Piot (Executive Director, UNAIDS), Carol Bellamy (Executive Director, UNICEF), Jacques-François Martin (President of The Vaccine Fund), Chris Hentschel (CEO of Medicines for Malaria), Jose Serra (Minister of Health for Brazil), Kiran Mazumdar-Shaw (Chairman and Managing Director of Biocon, India), Gillian Gresak (Director of AIDSLink, South Africa), Pascoal Mocumbi (Prime Minister

of Mozambique) and Hank McKinnell, Chairman and CEO of Pfizer.

The session’s participants were a mix of business leaders from the pharmaceutical, finance, media and mining sectors, among others.

Working in small groups, discussants considered the scenario as it related to one of three topics: capacity-building, with a focus on local vaccine manufacturing; financial, legal, and tariff issues; and improving distribution and delivery systems. Following the small group discussions, there was a lively report-back session, with one of the tables inviting Brundtland—a rapporteur from another table—to be part of its proposed activist movement, which would march in the streets for an AIDS vaccine.

Overall, participants advocated coordinated activity across many sectors. Key issues for the proposed action agenda include technology transfer, regulatory reform, process development for manufacturing large amounts of vaccine, and building or enhancing basic health-care infrastructure for vaccine delivery. At the core, they said, is the need to overhaul the usual “trickle-down” paradigm, in which developing countries receive vaccines long after they are licensed in rich countries.

To achieve this unprecedented goal, participants sketched possible new business models. Key components include: incentives and pricing mechanisms to increase private sector involvement in developing an AIDS vaccine; global harmonization of regulatory policies; and increased funding for projects that link health and development. They also emphasized the importance of approaching AIDS as a development issue requiring input from business, NGOs, philanthropic groups, UN agencies, governments and grass roots organizations.

To help move this agenda forward, the WEF Global Health Initiative and IAVI are adapting the workshop for use at WEF regional meetings in South Africa (5-7 June) and India (27-29 November) later in 2002. These meetings will highlight AIDS-related issues of importance to businesses in the developing world including workforce health and stability. Participants from these meetings will then convene at the 2003 global WEF meeting for a follow-up session to build on the accumulated momentum, and develop future activities. ♦

“At the core is the need to overhaul the usual ‘trickle-down’ paradigm, in which developing countries receive vaccines long after they are licensed in rich countries.”

arresting image, he spoke about the flight of trained young doctors and nurses personnel out of the country, which has been rocked by political unrest in recent years. Chandiwana says that he pleads with his medical students to remain in the country, telling them, "If science can survive at this lowest ebb in history, the future may be positive."

AAVP hopes to help address the need for highly skilled local personnel by boosting the capacity of African universities to train MS., PhD and post-doctoral candidates in vaccine science. In the short term, it will continue the established series of "wet workshops" and training courses offered with WHO/UNAIDS. These activities will enhance training from various bilateral partnerships around HIV and vaccines.

Such training is one of AAVP's strategic milestones, Esparza says, and one where he hopes that other collaborators will step in. One new player: the US HIV Vaccine Trials Network (HVTN), which recently appointed a coordinator to develop teaching materials for ten key areas, including HIV vaccinology, community advisory boards (CABs) and data management—a curriculum that could evolve into an accreditation process. At Johns Hopkins University, Karen Charron and Don Burke have developed an

Internet-based course ("Clinical Vaccine Trials: Planning and Implementation") given during the academic semester and drawing students from around the globe. Recently, it went on the road as a 3-day, hands-on workshop in Nairobi for staff of the Phase I vaccine trial co-sponsored by IAVI, the Kenyan AIDS Vaccine Initiative and the UK Medical Research Council; soon it goes to HVTN sites in Durban and Johannesburg.

Yet another capacity issue that AAVP will face comes from the growing needs around licensing and regulatory mechanisms. (See interview, page 10). And a group like AAVP has a role to play by emphasizing the importance of the issue, advocating for resources and referring personnel to relevant trainings.

Seizing Opportunities for Change

Despite these gaps, there's reason for optimism on the political front: The move towards pan-African vaccine advocacy comes at a time of unprecedented regional collaboration on the continent. Integration was the watchword at the third African Development Forum in Addis Ababa this March, and is a guiding principle for the Organization of African Unity (soon to be renamed the African Union.) "The general trend in Africa is for countries to work together much more

than they used to," says Gayle Smith, former senior advisor on Africa to the Clinton administration and an advisor to IAVI.

AAVP hopes to become a powerful and familiar presence in these networks. "We have to talk with African heads of state about the need to work together," says Uganda's Kaleebu. "We need a group doing advocacy with the South African Development Community (SADC), the OAU, and other groups. Their political commitment is necessary."

Whoever takes the helm of the newly formed African Union—South African president Thabo Mbeki has been touted as a likely candidate—will face the fact that AIDS is what Smith calls "one of five number one priorities" for Africa. Debt, war, TB, malaria and endemic poverty rank high on African political agendas and are inextricably linked to the several of the epidemic. Even here, though, there are reasons for optimism. Smith suggests that a regional or continental vaccine initiative might lobby for economy-boosting activities, such as in-country manufacture of vaccines. It might also explore conflict-resolution strategies—even temporary ones—that would allow vaccinations to take place within war zones. "AIDS is the best opportunity for structural change in Africa in ten to fifteen years." ♦

IAVI Announces Vaccine Partnership with Swedish Company

On May 6, 2002, IAVI announced a new vaccine development partnership (VDP) with the Swedish biotechnology firm, Bioption AB, to develop HIV vaccines based on a new delivery system made at Stockholm's Karolinska Institute. The vaccines will use emliki Forest Virus (SFV) replicons, which are genetically modified versions of SFV, a member of the alphavirus family. Alphaviruses have a broad host range and generally do not cause disease in humans, and the SFV vector has been engineered to attenuate the virus further.

One potential advantage of SFV and other alphaviruses is a self-amplifying replication pattern in which certain segments of the viral

genome are copied several times during a single replication cycle. This property could be useful in developing "dose-sparing" vaccination strategies, since more antigen could potentially be made by a given amount of vaccine. Additionally, SFV replicons cause programmed cell death after replication is completed, eliminating the risk of DNA integration into the cellular genome.

The IAVI-Bioption partnership aims to have an SFV-based candidate (based on HIV subtype C) in human trials within two years. It will also be tested head-to-head against other AIDS vaccines, including those using naked DNA or bacterial vectors, as a way of comparing different vaccine vectors. —EB

France's AIDS Vaccine Program

Michel Kazatchkine is director of France's Agence Nationale de Recherches sur le SIDA (ANRS) and head of Immunology at the Hôpital Européen Georges Pompidou in Paris. He is also President of the Technical Review Panel of the Global Fund against AIDS, Malaria and Tuberculosis and member of the WHO/UNAIDS AIDS Vaccine Advisory Committee, and advises EMEA,

Europe's regulatory agency for medicines and vaccines. After earning an MD at the University of Paris, Kazatchkine moved to St. Mary's Hospital in London as a research fellow, and later to Harvard Medical School in Boston. A few weeks before the latest Global Fund meeting, he met with IAVI Report editor Patricia Kahn in Paris to discuss France's work on AIDS vaccines.

AN
INTERVIEW
WITH

Michel
Kazatchkine

There aren't many European countries with a separate research agency dedicated to AIDS. How did this come about in France?

The decision was made back in 1992 to create the ANRS as an extraordinary agency, in the truest sense of the word, in response to an extraordinary epidemic. I think it is really as simple as that. INSERM, the agency that funds most biomedical research in France, works by supporting the best science, rather than by a more programmatic approach which prioritizes specific areas.

At that time, France was the European country most affected by AIDS, in terms of absolute numbers of people. Scientifically, we had enormous impact because of the discovery of the virus here in 1983, and then identification of CD4 cells as its targets. Also, activists organized themselves very early on. The complex interaction between the disease and the clinic, the society, community, patients, politicians—this happened very fast in France, as in the US.

All this put a lot of pressure on the authorities. It quickly became clear that an AIDS research program could not fit into INSERM's way of working. So the ANRS was created.

At one point a few years ago, that decision was re-visited. Why?

I took over in 1998, two years after HAART was introduced. People were very confident about the future of HAART. Jean-Paul Levy, my predecessor, thought that progress was so great from a basic science perspective that France did not necessarily need a specialized AIDS agency anymore.

However, we had built a well-running network of clinical centers that had done many studies. This is a unique example in France. So Levy thought that perhaps ANRS should become a national agency for conducting trials across all areas of clinical medicine.

At the same time, many people, including myself, thought it was too early to eliminate ANRS. Even though HAART had changed the lives of hundreds of thousands of people in the North, we were learning about its limits. We desperately need new families of antiretrovirals, and an enormous investment in basic science to find them. The interplay between the host and the virus is such that whenever something is achieved, within a few years we see its limits. I think this will continue until we either find drugs that eradicate the virus, which we do not

foresee right now, or we get a preventive vaccine.

And we were seeing the growing disaster in the developing world. I thought that France should play a key role in this battle, particularly since we have strong historical links with many developing countries.

What is the ANRS budget?

About 44 million Euros (US\$ 39 million). This comes on top of salaries and infrastructure, so you should roughly double that figure. It's still far from NIH's \$2.2 billion, but for a country the size of New York State, it's a large amount of money.

How is the ANRS vaccine program organized?

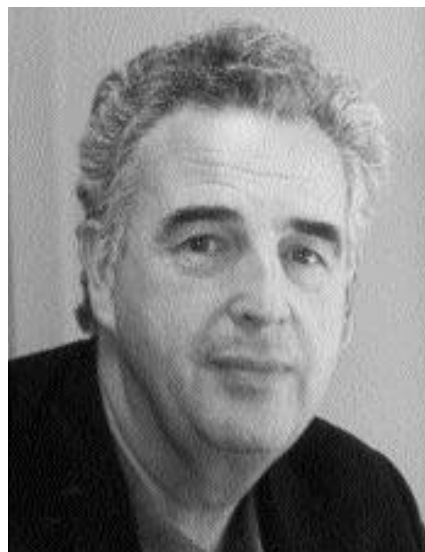
We have a separate clinical trials network for preventive vaccines—a French equivalent of the US HVTN (HIV Vaccine Trials Network). This network has six trial sites, a Phase I/II protocol committee and a network of volunteers. And we are now building up a few sites in the developing world.

We also have three core labs. One of them performs the cellular immunity assays. They have done a lot to standardize methods with the HVTN central lab in Seattle. For some previous trials we even did independent assessments of the same samples, and we will do this again in a forthcoming US trial of two products made here. We also have separate core facilities for assessing antibodies and mucosal responses.

What do you mean by a 'network of volunteers'?

Our volunteers are selected centrally in Paris by a multidisciplinary committee of physicians, sociologists, psychologists—not by the local investigator. Potential volunteers contact us, usually through ads in national media, and are selected based on clinical examinations and interviews. Those who are selected enter what we call our network of volunteers. Before a new trial starts, they are asked whether they wish to participate in that particular trial.

We want the volunteers to feel like part of a community. Once a year we organize a meeting to inform them about ongoing trials and plans for the future. There are cocktails, and a chance to mix



continued on 8 ▶

with the investigators.

How many trials are now going on?

We have done twelve Phase I/II trials of preventive vaccines. Two are ongoing, and three more will start within the next months.

France has put a lot of effort into developing the canarypox-based vaccines. What was your reaction to NIH's recent decision not to go forward with the Phase III trial of canarypox and gp120?

I'm actually not surprised. The problem is always the same. Either you only move forward when you think it's reasonable scientifically—but then you may wait forever. Or you move with small chances of success. As our Thai colleagues have said many times, if there is the slightest chance, let's do it—because if you don't, you'll never know. And the advantage of ALVAC is that it is a very well-studied vector with a lot of data available.

But many of us think that ALVAC with gp120 is not an optimal strategy. It doesn't induce broad neutralizing antibodies against primary strains, and we have better ways of getting cellular responses.

What surprised me, though, was that NIH's latest Phase II data showed much lower immunogenicity than previous ALVAC trials, including ours. We have wondered whether something in the assessment might explain this. But whatever you think about that, ALVAC plus protein is not the strategy we would push to Phase III.

What other types of vaccines are being developed in France?

Our overall goal is a vaccine based on inducing cellular immune responses through a prime-boost strategy, although we expect it to be only partial effective at first. Over the next three years we will choose the immunogens, the industry partners, and the way to delivering the vaccine, and then possibly test this in Phase III.

Our immunogen will be a mixture of lipopeptides plus a 'prime' component still to be chosen. [Editor's note: These lipopeptides carry key HIV epitopes plus a lipid group thought to enhance uptake by cells in vaccine recipients.]

Our past Phase I and II trials with lipopeptides show that even on their own they induce good CD4- and CD8-T-cell responses. In a trial finished last year (VAC 04) we saw responses in 75-85% of the volunteers, with many responding to multiple epitopes (*AIDS* 2001;15:1239). The responses lasted for at least a year after the final immunization. These are among the best results obtained so far in terms of cellular responses.

However, the strategy has some problems. Lipopeptides cannot easily be manufactured on a large scale, so our chemists are working to modify the chemical synthesis. Our plans for 2003 include a trial to compare the lipopeptides used in earlier trials

with a new generation encoding the same sequences but produced by more industrially feasible methods.

Hasn't there also been concern that the peptides might have too few epitopes, and not generate a broad enough response?

It is not less broad or broader than other approaches. We're using cocktails of five or six peptides, most of them from *gag*, *pol* and *nef*, with well-conserved epitopes known to stimulate strong cellular responses and bind well to class I MHC antigens.

But remember, the idea is to use lipopeptides as a boost, not on their own. For example with canarypox, the logic was to make constructs with HIV genes containing the same sequences as our peptides. We are now testing this combination in a Phase I prime-boost study called VAC 010, sponsored by Aventis Pasteur. And we are planning a Phase II study of this strategy through the HVTN.

ANRS and Aventis Pasteur have a long-standing partnership. Besides canarypox, what are you working on now?

Aventis Pasteur may become a closer partner in the lipopeptide venture. They are now negotiating with the French public system, which owns the lipopeptide patents. They are also working on NYVAC [an attenuated poxvirus vector], and have a strategy based on the HIV-*tat* gene.

Over the past two years we have changed our relationship with Aventis. Rather than just funding their work, as in the past, now we each bring money to a defined joint program, which is reviewed every six months. The current phase will end soon, and we have just started preliminary discussions about whether to continue.

If your public-private partnership with Aventis should yield a successful vaccine, what would be the implications for widespread access later on?

The contract includes a return of the public investment to ANRS. We have not yet discussed what we would ask in terms of delivery or distribution of the vaccine worldwide.

But I'm not too worried. I think the global community will be able to make these vaccines available to those who need them. Maybe I'm a bit of an optimist, but things are changing so fast with regard to drug prices and political awareness of the AIDS crisis. And don't forget that, although Aventis Pasteur is of course not Pasteur Mérieux, the tradition of philanthropy at Mérieux in terms of vaccines is an example to the world.

What are some of your other approaches, and who are your industry partners?

We worked with Biovector, who prepared the lipopeptides for our ongoing VAC 012 trial. We have a partnership with GlaxoSmithKline for a therapeutic vaccination trial with their protein-based vaccine and

are in discussions with Transgene about an MVA. We will start our first mucosal vaccine trial this year.

What will that trial test?

The rationale comes from studies of highly-exposed, uninfected sex workers. In Abidjan, we found that many of these women have HIV-specific antibodies in their cervico-vaginal secretions (CVS). So the trial will test whether mucosal antibodies can be induced by intranasal immunization with gp120 (from Aventis Pasteur) with or without adjuvant.

Antibodies purified from the CVS of these women do not have neutralizing capacity using conventional assays. But they inhibit the movement of HIV through a tight monolayer of cultured epithelial cells, a system which perhaps models sexual infection across the mucosa. So now the task is to identify the key epitopes that block this "transcytosis" of HIV.

The assay sounds tricky.

It is very cumbersome. You have to seal the chambers and grow the epithelial cell monolayers, and test them to make sure there are no holes. Then it takes hours for less than 1% of the virus put into the top chamber to get through. But the technique is now established in our core mucosal lab.

How will you do this in a larger trial?

We will need to build technology that can be scaled up. Scientists from our core mucosal lab are talking with some Canadian researchers who are also interested in this. But for these pilot trials we will use the craftsman type of techniques, just as in the first anti-retroviral trials people measured viremia by very cumbersome methods

You said earlier that ANRS is establishing trial sites in the developing world.

We started this two years ago with the Institut Pasteur, which has an international network of institutes in many developing countries. We are now building capacity for vaccine trials at three sites: Abidjan, Côte d'Ivoire; Dakar, Senegal; and in the future in Phnom Penh, Cambodia.

In Abidjan we now have a group of clinicians, plus virology and immunology capacity. Together with the Ministry of Public Education of the Côte d'Ivoire, we are starting a prospective cohort to gather HIV incidence rates and other data to help build the basis for a Phase III study. Volunteers are seen every six months and receive counseling and HIV testing, and are followed up by sociologists, anthropologists and epidemiologists.

Isn't there also a similar unit in Abidjan through the CDC (US Centers for Disease Control)?

Yes, there is a strong CDC program, the Rétro-CI program. Unfortunately, in past years the competition between the two groups was fierce. Especially

in vaccines, this can be very confusing for the general public. People at the CDC fully agree that this must be avoided, and we are now in close contact.

I'm still bitter about earlier times when ANRS and the CDC conducted the same mother-to-child prevention trials on the same site. The two trials gave the same results and were published in the same issue of the *Lancet*. So we reinforced each other's results. But if we had done one trial instead of two, 300 fewer women would have gotten placebos. We must learn the lessons from this.

The CDC group is pursuing Harriet Robinson's vaccine strategy [DNA/MVA prime-boost] and hopes to do Phase I and II tests. ANRS hopes to bring some small trials there early in 2003.

Are you working with local strains?

No. We're not pursuing a clade-specific strategy, but a sort of universal vaccine strategy. First and most obviously, this is because the map is changing so fast. Five years ago, Abidjan had only clade A. Now there are A/G recombinants. By the time we have a vaccine, the map will again be different.

We are also sequencing the circulating viruses and looking carefully at regions with T-cell epitopes, to help us select the best peptides for our vaccine. We also saw that T-cells from HIV-infected Ivoirian patients respond to clade B peptides much like HIV-infected people here in France. This echoes what Emilio Emini presented in Seattle [at the Retrovirus Conference; see *LAVI Report*, Jan/Feb 2002, p.1].

Once you choose your vaccines, how and where will you conduct a Phase III trial?

We have not devoted enough thinking to this. Nor do we have enough funds. Over the next three years, I hope that Europe gets stronger in this regard—for example, through the European Clinical Trials Platform, which would build trial capacity at a few developing country sites. We also hope to work with different organizations active in the developing world. We cannot go alone; we will need international support.

But ANRS is pushing only one of four or five approaches that should mature within a few years. There will also be DNA/MVA strategies from Harriet Robinson and Andrew McMichael, plus a Merck vaccine. We'll see how those compare. And it will be up to the international community to decide on what moves to Phase III.

That raises another issue. I strongly believe we need international consensus on how and when to go to Phase III. I said this at a meeting last year, and David Baltimore (Chair of the NIH's AIDS Vaccine Research Committee) answered, 'Michel, are you proposing another super-body? You know we're all fed up with big agencies.'

But I'm worried about what could happen if there are several Phase III candidates at the same time. How can a developing country decide, for

continued on 15 ►

Licensing an AIDS Vaccine in Developing Countries

AN INTERVIEW WITH

Julie Milstien



Julie Milstien is Coordinator of the Access to Technologies Team, Department of Vaccines and Biologicals at the World Health Organization (WHO) in Geneva. The team's mission is to remove barriers to making vaccines and immunization-related technologies widely accessible. Before joining WHO in 1988, she spent 14 years at the US

Food and Drug Administration. Milstien has a PhD in Biochemistry from the University of Southern California and did postdoctoral work at the National Institutes of Health. Here she and IAVI Report editor Patricia Kahn discuss some of the regulatory issues that will arise in making an AIDS vaccine available worldwide.

How do vaccines developed in the USA or Europe get approved for use in developing countries that don't have domestic agencies to license them?

This can work by different mechanisms. Some vaccines—especially older ones like DTP [diphtheria, tetanus and pertussis] or BCG, to some extent polio; oral polio—are also manufactured in certain developing countries, so they are eventually licensed there by national regulatory authorities. But those regulators don't really look at efficacy data based on their country's own epidemiological situation. Up to now they've just taken or adapted guidelines based on clinical data from the US or Europe.

For vaccines that reach developing countries through UN agencies—UNICEF, for instance, or the PAHO revolving fund—WHO is responsible for advising these agencies on which ones are acceptable to purchase. That involves an evaluation of the vaccine. But again, we find that for the most part, this evaluation is based on experience in the manufacturing country, not the countries importing the vaccine.

With some newer vaccines for example Hib, [Haemophilus influenzae type B] we're trying to ensure that the evaluating committees see clinical trials data reflecting local conditions—the immunization schedule that will be used locally; what other vaccines will be given at the same time; the local epidemic situation.

What kinds of regulatory obstacles or gaps could come into play with an AIDS vaccine?

I can't answer that question in general. It depends a lot on the circumstances. Without specific examples, it's difficult to ensure we've got all the gaps covered.

Here's one dilemma we have now: If an industrialized country makes a vaccine that will be used *only* in the developing world, how do you get it licensed?

The US and European agencies, the FDA and the EMEA, are responsible only for vaccines used in their domestic markets. Their mandate actually forbids them from giving marketing authorization to any vaccine that will *not* be marketed at home. So it's not for them to look into what happens with a vaccine used in African countries, for example.

Are there examples of vaccines that are now caught in this situation?

Not yet, although there is a potential example: vaccines based on a DTP [with whole cell pertussis] combination. These are manufactured in Europe but used only in one or two European countries. This is what keeps them licensed in Europe—although at the time they were licensed, nobody in Europe was planning to use them.

So how could they get licensed?

The EMEA decided to license them, since there was a possibility they might be used in Europe and because WHO thought this was really important. Just recently, EMEA renewed the license, because the vaccine is being used in Spain. But if Spain were to switch to acellular pertussis vaccine, then we would need another mechanism.

This is the real gap that could arise with a vaccine against AIDS or malaria.

What's being done to address this gap?

It's multi-pronged. First, WHO is working with the EMEA specifically to see if they will agree to consider giving, not a marketing authorization, but as near as they can come to one, to products that won't be sold in Europe. They recently agreed to this, and to assure ongoing regulatory oversight. Actually, when things go through the EMEA centrally, it's the country of manufacture that guarantees ongoing oversight.

This is a major step forward—it means that we have a solution for products made in Europe, provided that it holds up. We don't have it in writing yet.

For vaccines made in the US, the FDA says there really is no way they could do this. So we're looking at two alternatives. One is to better understand what are called the 'Export Provisions'—the rules under which the Secretary of Health allows unlicensed vaccines to be exported. That can be done if someone else takes responsibility for demonstrating the product's safety and efficacy. So vaccines can be exported in this way to, I believe, 26 countries, including those in the EU and the European Economic Space, as well as Canada, Japan, Israel, South Africa and Australia.

What about countries without the capacity to evaluate vaccines?

There would have to be a demonstration that the country had some mechanism in place for looking at

whether the vaccine is safe and effective. If not, we would need some other way to show this, and I don't know how that would work under the Export Provisions. We're still trying to pin down just when the Export Provisions would apply, and to understand all their in's and out's, and what kind of precedents have been set.

What would happen, then, if the first AIDS vaccine shown to work is based on a common East African subtype—so it probably wouldn't be licensed in industrialized countries—but the country that hosted the trial has no regulatory agency to license it?

Let's assume that most of these developing market vaccines would be bought by UNICEF or some other UN procurement agency. In that case, WHO has a responsibility to find a regulatory authority (RA), because our whole system of advising UNICEF depends on regulatory oversight. So we would find a way, somehow.

If it couldn't be licensed through the US, which it probably couldn't, then we would look at three other possibilities.

One is to export to another RA under the Export Provisions—for example South Africa, which has a full RA. But I don't mean to point to South Africa—we haven't discussed this with them or looked into it yet.

The second possibility is to look into licensing the vaccine as an orphan product. If there were a traveler's market in the US, or some kind of market—even a very small one—then it could be licensed in the US [and exported through WHO]. We haven't investigated this yet, but it's another possibility.

Another possibility is to work with manufacturers up front, looking carefully at how to plot the regulatory pathway for any promising vaccine down the line. The idea would be to make sure they have a partnership in a competent developing country that would do the filling, or finishing, or some other part of the manufacture, and then try to get the vaccine licensed there.

In all these cases, it's also essential to make sure that the licensing process includes expert input from the countries wanting to use the vaccine.

Are there efforts underway to build regulatory capacity in countries that lack licensing authorities?

WHO is very involved in strengthening National Regulatory Authorities (NRAs), through a relatively new system of assessments, based on indicators for evaluating how well an RA is functioning (see box). These, in turn, are based on the workings of WHO's Expert Committee on Biological Standardization plus inputs from 38 countries. The process includes a first assessment, followed by technical supports and training according to a plan that addresses the gaps, and then continued monitoring.

Between 1998 and April 2002 we've used this in 43 countries, and another 40-something assessments or follow-up are proposed for the next two years. The system has really been accepted by all the countries that have either supplied experts or been assessed.

Our first priority has been to assess countries that

manufacture vaccines, because they're the ones with ultimate responsibility for products being exported, as well as used at home. Of the 48 countries that manufacture vaccines, 30 have been found through this process to have fully functioning NRAs—for example, Brazil, Korea, Indonesia, South Africa, Russia, India.

Then there's another group of 8 or 10 countries that are fairly close to being fully functional, who we think will be there within the next couple of years.

A lot of these assessments have been done as part of WHO's role in advising UNICEF on whether a vaccine is appropriate for purchase, since this decision requires an NRA assessment. And these vaccines are reassessed every two years, which includes seeing if anything has changed in the NRA.

What about having regional RAs?

We are trying to develop regional advisory committees, and regional expertise in areas like disease burden and demonstration of safety and efficacy, that would inform the regulatory decisions in individual countries. So if you had a vaccine to be used in Kenya, for example, and the RA of Kenya is not ready to go through the whole process, they could rely on the advice of another RA and be sure—because of the expertise on the advisory committee—that it had considered the needs of Kenya and its neighboring countries.

We may have a case soon: the conjugate meningitis-A vaccines being developed for Africa. We'll probably have to use one of these regulatory pathways.

How can people in developing countries acquire this expertise?

I'm so glad you asked that! We have something called the Global Training Network on Vaccine Quality (www.who.int/vaccinesaccess/vaccines/Vaccine_Quality/gtn/gtn.htm). Right now it has 13 centers around the world, and they provide training in activities relating to regulatory oversight. It's a little different than the usual WHO training, because it requires an institutional development plan based on an RA, which will then build on this assessment process. The needs it identifies are then discussed with the country, along with what possible training or technical inputs might be implemented.

What topics does your training cover?

We have curricula in GMP, licensing, lot release, lab quality systems, different lab testing methods, and monitoring and dealing with adverse events. Later this year we will add a new one on clinical evaluation.

Is there anything vaccine developers can do early on to minimize regulatory delays or complications later?

My recommendation is to map out a regulatory strategy up front. Once you know who will make the vaccine and what its basic characteristics will be, then you think through how it can be licensed. Because this will impact where your clinical trials are held, how you want them set up, where your IRB is going to be—all these kinds of things. ♦

WHO CRITERIA FOR A FULLY FUNCTIONAL NATIONAL REGULATORY AUTHORITY:

- system to license vaccines, with regulatory enforcement power and legislation backing it up;
- monitoring of adverse events, including how to detect, investigate and resolve them, and to take regulatory action, if required;
- system of lot release;
- access to a competent laboratory;
- regular inspections to monitor compliance with good manufacturing practice;
- evaluation of clinical data.

*A One-Day Satellite Meeting on AIDS Vaccines at the
XIV International AIDS Conference*

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- ◆ Issues regarding access to and delivery of future vaccines
- ◆ Break-out discussions

Confirmed speakers include:

José Esparza, Don Francis, Lieve Fransen, Geeta Rao Gupta, Peggy Johnston, Michel Kazatchkine, Emmanuel Mugisha, John Shiver, Paulo Teixeira, Tim Tucker, Seth Berkley.

Registration:

To register, please visit IAVI's website at www.iavi.org/barcelona. Individuals from all sectors of HIV/AIDS-related work are welcome, but space is limited and registration will be monitored to ensure balance in regional and sectoral representation.

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aids vaccines



In the prime-boost study, McMichael reported on 6 volunteers from the DNA-HIVA trial received an MVA.HIV boost one year after their final DNA injection. All six showed responses after the boost. “The prime-boost might give a better mix of responses than either one alone,” said McMichael. The Oxford team is now conducting intracellular cytokine (ICC) assays for a closer qualitative analysis of the responding cells.

Similar DNA and MVA trials are being conducted in Nairobi, and the UK team has just begun a Phase IIa prime-boost study (see article, page 1).

NIH-sponsored Trials

Rounding out the human trials session, Barney Graham (VRC, Bethesda) began with data from HVTN 203, the Phase II trial that was pivotal in NIH’s decision not to move into efficacy trials with this prime-boost strategy, which combines the canarypox-based ALVAC vCP1452 vaccine with a gp120 boost. (In Thailand, Phase III plans for a prime-boost trial of another ALVAC vaccine plus gp120 are continuing, although this trial was not discussed by any Keystone presenters.) Six months after the last immunization, only about 16% of the vaccinated volunteers showed T-cell responses against HIV Env or Gag, as measured by cell-killing assays (see Table 1). Graham did not present ELISPOT data, but said that interim results appeared “no better” in terms of immunogenicity.

He then described future trial plans for the VRC, which is working on a DNA-adenovirus strategy similar to Merck’s. Within the next few months, they will launch a Phase I trial of a DNA-gag prime delivered via Biojector, a needle-free delivery system, and a boost of recombinant adenovirus (rAD) containing *env* from clades A, B and C, delivered both intramuscularly (IM) and intranasally (IN). Building on the VRC’s DNA-gag-pol vaccine now in Phase I studies, new DNA and adenovirus constructs will include HIV-gag, pol nef and *env* from clades A, B & C. Graham said that the VRC is pursuing a “multivalent, multiclade” approach.

NON-HUMAN PRIMATE STUDIES

Wyeth Ayerst’s HIV-VSV Vaccines

Last year, John Rose from Yale University published encouraging protection data on an SIV vaccine made in a vesicular stomatitis virus (VSV) vector (*Cell* 2001;106:539-549). At Keystone, Michael Egan from Wyeth Ayerst (the company that has now licensed the VSV platform) presented a new study comparing mucosal vaccination (IN) to the earlier IM immunization protocol (see details in Table 2) in ten macaques, which were then challenged intravaginally with the pathogenic HIV/SIV hybrid SHIV89.6P.

Overall, they found that animals immunized IN had higher levels of pre-challenge cellular immune responses to SIV (measured by tetramer staining and ELISPOT) compared with the IM group, as well as

somewhat better post-challenge control of peak viral load and preservation of CD4 counts. Antibody titers were similar in both vaccinated groups, and (unusually) all animals—except one control which died by 150 days post-challenge—showed similarly low viral set points. Based on these data, Egan concluded that IN administration is the preferred delivery method for this vaccine. Wyeth Ayerst is continuing to develop the VSV platform for potential human use.

In Search of AAV

Last year at Keystone, Phil Johnson (Children’s Research Institute, Columbus) showed promising macaque data on an HIV vaccine made in Adeno-Associated Virus (AAV), a harmless virus widespread in human populations (see *LAVI Report* Feb/Mar 2001). The potential advantage of AAV vectors is that they persistently express foreign genes—at least 17 months has been seen in macaques—and might therefore work as single-dose vaccines. However, a key safety issue is whether the vector integrates into the host cell genome, which could have unknown consequences.

This year, Johnson presented data showing that the AAV-SIV vaccine does not appear to integrate into the DNA of immunized mice. Using a battery of different tests, his team found no integrated AAV in muscle cells at the injection site, indicating that over 99.5% of the vector molecules that persist are unintegrated, said Johnson, and “in the same ballpark as plasmid DNA vaccines.”

Johnson concluded by outlining a novel strategy for combining HIV-specific cellular immune responses and neutralizing antibodies (NAb) in macaques—the combination widely viewed as a “next-generation” HIV vaccine. Since no vaccine so far has induced broad Nabs against primary strains of virus, Johnson and collaborators Dennis Burton and Paul Parren (Scripps Research Institute, La Jolla) instead took an existing one—a monoclonal antibody called b12, derived from an HIV-infected person—and inserted the DNA encoding it into AAV vectors. Immunodeficient mice injected with these constructs

continued on 14 ▶

Table 1: HVTN 203 Immunogenicity Results (Day 182)

Test Antigen/volunteer group	Response*
Env vaccine placebo	8/122 (7%) 0/51
Gag vaccine placebo	16/122 (13%) 1/53
Env or Gag vaccine placebo	20/124 (16%) 1/53

* number and % of volunteers (relative to total number tested) showing HIV-specific CD8 T-cell responses, as measured by standard cytotoxic lymphocyte assays (⁵¹Cr-release) on fresh PBMCs, 182 days after the last immunization

Table 2: Effect of HIV-VSV immunization on CD4 counts*

Study Group	CD4 cell count (% of baseline) at 150 days in each animal
IM group vaccinated (n = 3) control (n = 2)	86, 76, 47 21, other animal died < day 150
IN group vaccinated control (n = 2)	102, 92, 83 104, 28

*Animals were immunized at 0, 8 and 16 weeks with VSV vectors encoding SIV Gag and HIV Env genes and challenged intravaginally with SHIV89.6P at week 21. Data show CD4 counts from individual animals, 150 days after challenge.

have so far shown sustained b12 expression for over six months. Johnson is now looking to test this b12-AAV vector together with his existing HIV-AAV vaccine, which induces cellular responses, and develop the combination as a human vaccine.

T-cell Responses, Viral Escape and Avidity

David Watkins (Wisconsin Primate Center) presented data on HIV escape in three macaques that became infected despite vaccination. The animals (all MamuA*01) had received a series of immunizations with DNA and MVA constructs encoding the epitopes Gag CM9, Tat SL8 and whole Tat, Rev and Nef proteins. The choice of immunogens was based on a long-term non-progressor monkey that had CD8 cells directed against these epitopes (plus CD4 T-cells targeting Rev, Nef and Gag); moreover, the CD8 cells bound these epitopes with high avidity, which Watkins has correlated with the emergence of SIV escape mutants in infected animals. He therefore reasoned that inducing these responses in animals prior to challenge—in effect giving them a head start over SIV—might induce effective immunity. Twenty weeks after the last immunization, animals were given a high-dose i.v. challenge with SIVmac239. But, despite an initial reduction in peak viral load, all animals had high levels of viremia by week 18, along with SIV escape mutations in the CM9 and SL8 epitopes.

Watkins also showed that this vaccine failure occurred despite indications that the animals had HIV-specific mucosal responses. About 12% of T-cells in the gut and 8% in blood expressed a cell surface molecule, alpha4-beta7, associated with cells trafficking to the mucosae.

James Allison (University of California, Berkeley) offered another perspective on avidity and epitope selection. Allison found that high-avidity binding is associated with the up-regulation of CTLA-4, a cell surface molecule that stops T-cell replication. Allison speculated that this may help increase the diversity of immune responses by shutting down the proliferation of T-cells binding to high-avidity epitopes, thus leaving room for subdominant responses to emerge.

ENIGMAS OF NATURAL CONTROL AND PROTECTION

Continuing the theme of identifying immune parameters of viral control, Brigitte Autran (Hôpital Pitié-Salpêtrière) described recent results from her group's extensive studies on long-term non-progressors (LNTP) and outlined how these findings are being used in developing therapeutic vaccines.

In terms of cellular immunity, control of viral load in LNTP correlated with high levels of HIV-specific CD4 cells (those producing IFN-gamma), and, to a lesser extent, with the intensity and diversity of CD8 T-cell responses. Non-progression also correlated with levels of IgG2 antibodies directed against Gag and gp41 (*AIDS Res. Hum. Retroviruses*: 2001;17:1435). Whatever role these antibodies play (they do not appear to be neutralizing), Autran proposes that they may give data on T-cell functionality not captured by IFN-gamma alone. Overall, the combination of IgG2 and HIV-specific CD4 responses were the best predictors of LNTP status.

Autran's talk finished by reviewing efforts to enhance CD4 responses in infected people on HAART, using canarypox-based HIV vaccines (ALVAC vCP1433 or vCP1452) with or without a whole-killed HIV vaccine (Remune®, originally developed by Jonas Salk). After one or two injections, 65-75% of the 200 volunteers had detectable T-helper responses (50-800 spot-forming cells in chronically infected people given ALVAC, 50-1500 SFC in acutely infected people given ALVAC or both vaccines). Autran, who plans similar trials with newer vaccines, added wryly that therapeutic vaccination is "*Elysienne* [like heaven]—we always talk about it, but never see it."

In the same session, Bruce Walker presented a prospective, blinded study of Zambian serodiscordant couples. Walker and a team led by Marilyn Addo analyzed samples from 36 individuals, 25 of whom were defined as high-risk due to being in serodiscordant couples, and found no evidence of anti-HIV responses at the first time point or one year later. Walker concluded with the bold suggestion that "There are no CTL responses in HEPS [highly exposed, persistently seronegative people]—that's our feeling based on the data we have." Of note, the study criterion for high exposure was 3-4 high-risk sexual events per month—much less than the 6-7 exposures per day or week seen in other HEPS cohorts, such as the Nairobi sex worker group, a difference that could explain the absence of responses in this study.

In another session, Sarah Fidler (Imperial College Faculty of Medicine, London) presented a UK-based study of 20 predominantly homosexual male couples showing that 13/14 had quantifiable HIV-specific CTL on at least one occasion. Here, highly-exposed individuals were defined as those who had 2 to 3 acts of unprotected, receptive anal or vaginal intercourse per week.

Table 3: Immune Responses* in Blood and Breastmilk

	Blood	Breastmilk	Milk + / Blood -
2 week env	23/35** (66%)	12/35 (34%)	3/10 (30%)
2 week gag	15/35 (52%)	9/35 (31%)	0/10 (0%)
4 week env	15/35 (52%)	9/35 (31%)	3/12 (25%)
4 week gag	11/21 (52%)	3/21 (14%)	2/14 (14%)

* Immune responses were measured on CD8 lymphocytes using an ELISPOT assay for IFN-gamma. A positive result = PHA stimulation >100 SFU/106.

** Number showing positive T-cell response/total number of volunteers.

BEYOND INTERFERON-GAMMA?

From Ahmed to Aufran, presenters echoed the need to define the most important functional markers associated with protection or immune control of HIV. IFN-gamma production is now commonly used to detect the presence of immune-activated T-cells in vaccine trials, but several presentations suggested that other markers may also be informative. For example, Ahmed pointed out that CD8 T-cells continue to produce IFN-gamma long after they lose other key functions, such as ability to proliferate or to produce IL-2 and TNF-alpha—suggesting that IFN-gamma may detect not only fully active T-cells but also functionally “exhausted” ones. Ahmed’s thinking is echoed in a recent paper from Norman Letvin’s laboratory (Harvard University, Cambridge) which showed that protection from disease progression in SIV-infected macaques correlates with the presence SIV-specific CD8 cells producing both IL-2 and TNF-alpha (*J. Immunol.* 2002;168:332-337).

Backing this up, a poster by Helen Horton (Fred Hutchinson Cancer Research Center, Seattle) compared results of classical cell killing (⁵¹Cr-release) assays and IFN-gamma production measured by ELISPOT, concluding that T-cells which produce IFN-gamma after antigen stimulation are not always able to kill target cells.

What other markers might play a role? Mark Boaz and colleagues from Kings College School of Medicine (London) characterized the HIV-specific CD4 T-cell responses in 16 long-term non-progressors (LTNPs) and compared them to 15 patients with progressive disease. LTNPs turned out to have significantly more cells expressing both IFN-

gamma and IL-2. The two groups showed no difference in the proportion of T-cells expressing IFN-gamma only.

MUCOSAL IMMUNITY

Mucosal immunologists complemented the marker-hunters with more data on HIV immunity in compartments other than blood. Yan Ding from Juliana McElrath’s group (University of Washington, Seattle) looked at CD8 T cells cloned from the blood, rectum and cervix of 12 (10M/2F) sexually-infected long-term LTNP and found that cells from these different compartments shared features such as epitope specificities and MHC restriction patterns. This suggests a common origin as well as trafficking between blood and mucosa, in contrast to several other studies that found distinct populations in the two compartments. To see whether her finding is specific to LTNP, Ding will do the same analysis in chronically infected individuals.

Another view came from Barbara Lohman (University of Nairobi) who showed that T-cell populations from blood and breastmilk of HIV-infected women differ in the proportion that respond to specific HIV antigens (see Table 3), suggesting some degree of separation between the compartments. ♦

Richard Jefferys is Basic Science Project Director at the Treatment Action Group, a New York-based organization advocating for HIV research (www.aidsinfonyc.org/tag). He was previously director of the Access Project at the AIDS Treatment Data Network, and most recently worked as a writer for the IAVI Report.

◀ KAZATCHKINE INTERVIEW continued from 9

example, whether to go with ANRS or CDC or both? Or imagine that a company comes and says, ‘You should do our trial. We will pay you more.’

How could a consensus ever be reached?

People should agree on a set of criteria that would have to be fulfilled. And we need to think about what sort of consensus body could be established. I’m strongly convinced that there are ethical risks if we do not have such a body.

Turning to the issues facing the Global Fund, in the past you have criticized the North’s weak response to AIDS in the South, especially the view that antiretroviral treatment is not feasible and should take a back seat to prevention.

It’s not only me—it’s also French politicians such as our present health minister, Bernard Kouchner, scientists; and the French community in general. We absolutely must avoid putting treatment against prevention. France has strongly advocated expanded access to treatment, for many reasons. First, why

should one set of standards apply to the North and another to the South? Second, if you wait until you have the capacity to treat 30 million people, you’ll never do anything. You have to start somewhere.

ANRS is conducting the first ARV trials in chronically infected people in Africa, in Senegal. We find that compliance is the same as in the North, and that our clinical results are also similar. And we see that ARV treatment contributes to de-stigmatizing the disease.

In Africa, the stigma is death, not sex. Showing that you can fight against death is a very strong way of de-stigmatizing AIDS in Africa.

Sometimes people say there is too much emphasis on treatment and not enough on prevention. In speaking and writing, and at the Global Fund, I emphasize treatment because so many people are still not convinced it can work. I oppose it when people say that treatment is not cost-effective, but condoms are. There are now examples to back me up, and we have to fight against this sort of statement.

But this also shows that an enormously expanded effort on vaccines is absolutely essential. ♦

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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. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

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Firsts for the Global Fund

The Board of Directors of the Global Fund to Fight AIDS, Tuberculosis and Malaria met in New York City for three marathon days (22-24 April) to make its first funding decisions and further define its mission. The Board approved US\$ 378 million over two years to 40 programs in 31 countries. A second round of 18 proposals from 12 countries may receive \$238 million, contingent on substantial changes and clarifications.

The first round of funding disbursements drew mixed responses, as praise for the new infusion of money mingled with concern that few of the proposals included interventions like antiretroviral treatment and first-line treatments for drug-resistant tuberculosis and malaria that are recognized as essential components of an effective, integrated response to these epidemics. Virtually all involved agreed that more money is needed. The Fund currently has pledges for \$2 billion to fight all three diseases—a small portion of the \$7-10 billion in global spending called for by UN Secretary General Kofi Annan just to fight HIV/AIDS.

The Board also selected its first permanent executive director, Dr. Richard Feachem, founding director of the Institute for Global Health (Berkeley, California) and former Director and Senior Advisor for Health Nutrition and Population at the World Bank from 1995 to 1999. Feachem is expected to take the helm in July 2002, with interim executive director Anders Nordström serving until then. Also in July, the Fund plans to release revised guidelines for the second round of funding, which will be decided upon in late 2002.

Novel "Pre-Screening" Study Starts in Soweto

How do you find low-risk volunteers for HIV vaccine trials in a community where up to 30% of its members are already infected? This March, the Vaccine Trials Unit (VTU) at Chris Hani Baragwanath Hospital in Soweto, South Africa, launched an innovative "prescreening" protocol addressing this conundrum.

Designed by VTU head Efithya Vardas and colleagues, the protocol offers adults voluntary counseling and testing at centers in Johannesburg and Soweto. After an initial negative test, interested volunteers are invited to enroll in the full protocol, which involves monthly testing (with pre- and post-test counseling) for HIV and STIs and bi-weekly "vaccine discussion groups" that cover vaccine trials from soup to nuts. (Vardas says that the protocol originally called for one meeting per month, but the community wanted more.)

After six months, HIV-negative participants will be offered enrollment in the site's planned vaccine trials (several potential candidates are being considered for Phase I studies). Those in the protocol who test positive can attend an HIV-positive support group and receive referrals to local care centers.

The protocol aims to enroll 40 individuals a month. Already on board: teachers, social workers and a Catholic priest.

India Announces First-Ever National AIDS Policy

On 4 April 2002, India—a country where nearly 4 million people are living with HIV/AIDS—released its first national AIDS policy. The document reflects a fundamental shift in the government's view of the AIDS epidemic, away from a crisis affecting only public health to "a developmental issue with deep socio-economic implications."

The comprehensive National AIDS Prevention and Control Policy (NAPCP) (naco.nic.in/vsnaco/nacp/ctrlpol.htm) builds on lessons learned from a recently-concluded "phase I" program of the National AIDS Control Organisation (NACO). It stresses that, while the federal government must take the lead in forging a response to the epidemic, program implementation must be decentralized to the State and local levels.

The policy provides a framework for improving support of infected people and expanding prevention efforts to include more comprehensive surveillance and universal access to treatments that reduce mother-to-child transmission. But its overriding message is the need for a multisectoral, "holistic" approach to the crisis, demanding deepened commitment across government branches, NGO's and international groups.

Candid in its recognition of the devastating effects of social stigmatization and discrimination against PLWHA's, the NAPCP also seeks to provide stronger legislative, legal and social protections for human rights. It also calls for access to palliative care and drugs to treat opportunistic infections, but does not include plans for expanding access to anti-retroviral drugs.

Annexed to the NAPCP was a new National Blood Policy mandating tighter regulation of blood banks and screening. HIV-contaminated blood accounts for nearly 4% of all new infections in India.

Thailand Reconstitutes AIDS Vaccine Subcommittee

On 13 March 2002, Thailand officially appointed a new Subcommittee for HIV/AIDS Vaccine Development and Trials, replacing the group which dissolved nearly a year ago in the wake of controversy over a proposed therapeutic vaccination study (see *IAVI Report*, Dec 2000/Jan 2001, p.20). The move comes not a moment too soon, with the country planning to launch its second Phase III trial later this year in southern Thailand (as a collaboration of the US Army vaccine program, Thailand's Royal Army and Ministry of Health).

The Subcommittee is chaired by Prasert Thongcharoen of Mahidol University, a leading virologist and central figure in Thailand's early, aggressive response to AIDS, which included a strong commitment to vaccine development. The group's six additional members bring expertise in areas ranging from immunology, infectious disease and epidemiology to family planning, women's development and human rights.

The subcommittee's immediate task is to review the protocol for the upcoming Phase III trial, which will test a prime-boost combination of a canarypox-based HIV vaccine (ALVAC vCP152) and gp120, in a community-based cohort of nearly 15,000 volunteers. The WHO/UNAIDS Group on HIV Vaccines will also provide an informal review, and submissions to the relevant Institutional Review Boards in Thailand and the US have begun.

As for the difficulties that led to the committee's dissolution, it now appears that the controversial vaccine Remune® will henceforth be treated in Thailand as a drug, not a vaccine—sending it down a separate regulatory path.