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A Global Health Fund: One Step Closer

BY SAUL WALKER

As delegates from around the world gather in New York for the United Nations Special Session on AIDS (UNGASS, 25-27 June 2001), efforts to establish a global fund to help bankroll international action against infectious diseases in developing countries are showing results.

While plans for such a fund are only now moving into the limelight, they have actually been evolving gradually over the past year, as various international forums have focused on the need for new financing mechanisms to combat disease and improve health in poor nations.

The idea began to gather momentum in July 2000 at the World AIDS Conference in Durban and the Okinawa meeting of G8 nations, who agreed to the proposal for joint action directed at HIV, TB, and malaria. Thereafter, similar ideas were proposed in several other arenas: the "Ottawa Group" (UK, US, Canada, and the European Union) began developing financing proposals directed at communicable diseases (which make up 60% of the disease burden in developing countries), while in February, Italy (the current G8 chair) announced its own proposal. In parallel, proposals for an HIV-specific fund have been advanced by the US, UNAIDS, and UN Secretary General Kofi Annan, who presented a version emphasizing AIDS in Africa at the April OAU summit (Organization of African Unity) in Abuja, Nigeria.

As people come together at UNGASS, there appears to be convergence on establishing a single Global Health Trust Fund focused initially on HIV, tuberculosis (TB), and malaria. Pledges to the fund have been made by the governments of the US (US$ 200 million) and France ($130 million); the UK has indicated probable support of $105 million, and Japan is also considering a contribution. Winterthur, an insurance subsidiary of the Credit Suisse financial services group, has made the first pledge from the private sector, for $1 million.

It is currently unclear how much the Fund will contribute towards the $7-10 billion which Kofi Annan estimates is needed from all sources to provide comprehensive HIV prevention and care in developing countries. (Present estimates range from $1-$3 billion.) Additional costs for TB and malaria are estimated at approximately $2 billion. The bulk of the financing for HIV/AIDS responses will con-

continued on 2 ▶

NEW STUDIES HELP PUT MUCOSAL IMMUNITY ON THE RADAR

BY EMILY BASS

The human body's mucosal surfaces—a vast immunological territory with a surface area equivalent to one and a half basketball courts—are its first immune barriers to the outside world. As such, they are thought to play a key role in susceptibility to HIV. And with over 80% of HIV infections transmitted sexually, meaning that they begin with virus crossing a mucosal surface in the genitals or rectum, immune responses at these borders could be a critical component of vaccine-induced protection.

But despite its potential importance, there are relatively few studies on mucosal immunity against HIV, making it hard to fit into the big picture of protection. That's largely because analysis of mucosal immune activity (particularly cell-mediated responses) requires invasive procedures—unlike systemic immune responses, which are easily measured from blood samples. Not surprisingly, AIDS vaccine trials have not focused on delivery of vaccine to mucosal surfaces and rarely include mucosal sampling, so there is almost nothing known about whether current vaccine candidates stimulate local responses.

In recent months, however, new research has helped bring some key issues into focus. Novel

continued on 17 ▶

Inside:

UN Draft Declaration 2

Haiti: AIDS Vaccine Trial Begins 3

AIDS Vaccine Tax Legislation Proposed in U.S. and U.K. 7

Laying Groundwork for AIDS Vaccines in Developing Countries: An Interview with José Esperaza 9

A New Research Center Tackles AIDS Vaccines: An Interview with Gary Nabel 13

Vaccine Briefs 20

◀ **GLOBAL HEALTH FUND** *continued from 1*

tinue to be channeled through existing national, bilateral, and multinational mechanisms.

Emerging agreement

The first meeting that brought together a broad range of players (developing and industrialized country governments, multilaterals, and a few NGOs) to discuss Fund proposals took place in Geneva on 3–4 June. Although this meeting was not designed to forge consensus on details of the Fund, there was agreement on some general principles:

- A single Fund will be established, rather than having different donors establish financing mechanisms for overlapping purposes.
- The Fund should have a number of separate "windows" which earmark money for specific purposes. One window will finance national and possibly regional responses to HIV; also proposed are windows for TB and malaria, and possibly a window for commodity purchase, covering both prevention and therapeutics (such as medicines and condoms). The issue of funding for antiretrovirals has yet to be agreed upon.
- The Fund should supplement, rather than replace, existing mechanisms, and should not be seen as the sole source of new money for tackling these diseases. National, bilateral, and multilateral efforts still urgently require scale-up.
- The operation of the Fund should not create unnecessary new bureaucracies or systems, but should place a premium on accountability, transparency, and the achievement of demonstrable outcomes.

Remaining questions

As the *IAVI Report* went to press, there was still no consensus on exactly what the Fund should be used for or how it can add value beyond simply increasing investment in existing mechanisms. For example, some donors favor more of a focus on commodities, using high volume to leverage better prices, and possibly on technical assistance to use the medicines in an effective, sustainable manner. Equally essential development of healthcare systems would work through existing mechanisms. In contrast, others (including the US) support a broader focus on both medicines and healthcare infrastructure.

Nor is there consensus on who will control or administer the Fund and where money will be held. The World Bank has been proposed as the banking facility, but some donor countries oppose this suggestion. There is similar caution on the role of the

continued on 6 ▶

Content of Draft Declaration Unresolved in Run-up to United Nations Special Session on AIDS

BY ABIGAIL BING

For the first time in the 20-year history of AIDS, the United Nations General Assembly has convened a special session dedicated exclusively to addressing the global epidemic. National delegates from the highest political levels, including at least a dozen heads of state, will gather in New York from 25--27 June 2001, in an attempt to intensify international action and mobilize resources to respond to the global crisis.

The meeting, designated the United Nations General Assembly Special Session (UNGASS), will focus on four themes: HIV prevention and care (including vaccine development), human rights, the social and economic impact of AIDS, and international funding and cooperation. A primary objective of the session is to gain General Assembly approval of a Declaration of Commitment on HIV/AIDS outlining key activities and establishing concrete targets for progress.

However, this is proving difficult. Drafts of the Declaration released in late February and early May drew criticism from government officials, public health experts, and AIDS advocates alike. Critics argued that the drafts failed to express the urgency of the AIDS crisis or establish sufficiently concrete actions and targets.

In a May preparatory meeting for UNGASS, General Assembly delegates gathered in New York to seek preliminary agreement on the draft's content. Although the latest version had not been publicly released when the *IAVI Report* went to press, sources say there have been significant improvements.

The draft reportedly now includes language encouraging increased investment in HIV/AIDS-related research, especially for the development of prevention technologies such as vaccines and microbicides. It also includes a call to make AIDS vaccines, once they are developed, available to all who need them. Strong support for the vaccine language reportedly came from southern African nations (the Southern African Development Community), Latin America (the Rio Group), and the European Union.

However, there was growing concern that the declaration will not receive approval from the entire General Assembly. Controversy surrounding human rights issues and the mention of specific vulnerable groups such as commercial sex workers, injection drug users, and men who have sex with men, have become obstacles to gaining sufficiently widespread support. Some countries have suggested they will refuse to sign a document that mentions these groups, while others may refuse to support a document that omits them.

Commenting on the controversy, Richard Burzynski, director of the International Council of AIDS Service Organizations, said that leaving out references to human rights and vulnerable groups "would undermine all the hard work that has gone into preparing the Declaration and result in a watered-down Declaration of limited usefulness."

Haiti: Scaling The Mountains

AIDS VACCINE TRIAL BEGINS IN THE WESTERN HEMISPHERE'S HARDEST-HIT COUNTRY

BY ANNE-CHRISTINE D'ADESKY

There is a Creole proverb that has long been a metaphor for Haiti's struggles: *Deye mon, genyen mon*—Beyond mountains, more mountains. From above, the island appears as a jagged range of overlapping barren crests completely denuded of trees—somber evidence of this once-lush Caribbean nation's steady decline into abject poverty. The loss of its forests was both a cause and a result: as poor Haitians cut down trees to get wood for cooking fires, the soil left behind could no longer hold water, turning the country into a dust bowl that is unable to grow enough food. Today, the world's first independent black republic is the poorest country in the Western Hemisphere, with an annual per capita income of less than US$ 300. High on the mountains, rural villages offer scenes of poverty so dire they vie with images from sub-Saharan Africa or the slums of India. Hunger is everywhere and so is AIDS: with 8 million people in Haiti, nearly 400,000 have HIV—the highest prevalence rate outside of Africa.

Yet there is renewed hope on many fronts. Earlier this year, President, Jean-Bertrand Aristide, a firebrand populist leader, took office for the second time and has vowed to lift up the country. Although the political situation remains rocky, the new government has energized efforts to tackle Haiti's thorniest problems, from a crumbling physical infrastructure to the AIDS epidemic.

With this new political backing, Haiti's efforts to build an HIV vaccine program reached an important milestone on 27 March: immunization of the first two volunteers in the country's first HIV vaccine clinical trial, at a treatment and research clinic run by GHESKIO (the Haitian Study Group on Opportunistic Infections and Kaposi's Sarcoma) in Port-au-Prince. The Phase II trial, a test of the canarypox ALVAC vCP205 vaccine, with or without a boost of VaxGen's gp120 protein, is being carried out under the auspices of the NIH's HIV Vaccine Trials Network (HVTN) at sites in Haiti, Brazil, and Trinidad/Tobago, with 40 low-risk volunteers at each of the three sites.

For the GHESKIO clinic and its energetic director, physician Jean Pape, the hope is that this study will be the first of many, and a prelude to a Phase III efficacy trial—as well as a model for how to do high-quality clinical research under the dire conditions common to many developing countries. "For now, we are getting our feet wet," he says. "We are going to do the Phase II and show that we have the infrastructure for a bigger trial, for a Phase III." That means confronting such deep-seated problems as a weak health infrastructure, a shattered economy, high unemployment, residual political instability, and a 70% rate of illiteracy, as well as anticipating daily logistical hurdles like bad roads, telephone lines and energy blackouts.

Pape remains unfazed by these obstacles. "There have always been problems in Haiti and we have always worked, often without a net," he says matter-of-factly. "These are not reasons to not move ahead. You must build the infrastructure and train the people. That can be done. In fact, that is what we are doing."

In preparing for the trial, the Haitian team has relied on a formula that has served them well: pragmatism, a public avoidance of politics, flexibility, close collaboration with outside partners and—a key factor—transparency. They've paid particular attention to informing community and political leaders about their research activities in advance, and to educating the media, who are now crucial allies. The clinic also works closely with several longtime collaborators from abroad, including Cornell University Medical College (Ithaca, NY, Pape's alma mater), the University of Michigan (Ann Arbor) and Vanderbilt University (Nashville, Tennessee), a "parent" site for the current trial.

Physician Jean Pape, a principal investigator of the vaccine trial

Pape also cites high-level political will as a key factor. "From the beginning, the Haitian government made it clear that they want to go to Phase III trials," he explains. "Aristide himself is very interested. He sees the suffering caused by AIDS and he wants to do something. So do all four of Haiti's recent health ministers and the entire cabinet."

One of them is Gabriel Thimothe, head of the Haitian Medical Association and a former Minister of Public Health, who began pushing Haiti's HIV vaccine effort a decade ago. In 1991, a United Nations mission visited the country to evaluate its potential for doing trials, but prospects then dimmed as Haiti's political climate became more unstable. A decade later, Thimothe remains convinced of the need for Haiti to play a role. "I believe the vaccine project can benefit the Haitian community facing the burden of high prevalence and the socioeconomic impact of AIDS," he says. "Behavioral change is so slow. It's time to act to avoid a catastrophe among the young population." In pushing the vaccine agenda politically, he also

stresses the economic argument. "We must focus on the cost efficacy of a vaccine compared to therapy," he says.

Paving the way

The road to the ALVAC trial has been long and rocky. It began in 1979 when Pape, then working on typhoid fever in Warren Johnson's lab at Cornell, decided to return to Haiti and start a Cornell program on infantile diarrhea, still a leading killer of children there. In 1982, when a strange wasting disease began killing many Haitians, he and a few colleagues formed GHESKIO as a research group to study the phenomenon, again with Cornell's backing.

At that time, Haiti's infamous dictator, "Baby Doc" Duvalier was still in power, the country was in turmoil, and there was little foreign aid. AIDS, as it was later identified, was a stigma, a public pox on Haitians, homosexuals, heroin users and hemophiliacs—the so-called "4 H's," as the media dubbed it. GHESKIO set up its small operation as a research and training facility at the National Institute of Laboratories and Research in the capital, on a road that degenerates into potholes and dust as it leads to the teeming "bidonvilles" where thousands of people live in a maze of tin roofs and mud paths without electricity or clean water.

"In 1983, we had a small microscope, an incubator, and a standard centrifuge," recalls Cornell's Johnson. "We could do a standard blood test, stool and urine, but not a hell of a lot more."

Over the next decade, GHESKIO struggled to track the epidemic and initiate community education and prevention programs along with HIV testing and counseling. By 1994, the team had established several low and high-risk HIV-negative cohorts, including one with 500 people from serodiscordant couples (HIV-negative sexual partners of positive individuals) and another with HIV-negative women attending the STD clinic.

Pape's group remained active during the difficult years that followed, carrying out two surveys of community attitudes about HIV vaccines—information later used to establish informed consent procedures for the current trial—and continuing to gain experience in caring for people with AIDS, many of whom also had tuberculosis and/or STDs. More recently they expanded their laboratory and clinic space, thanks to grants from Japanese and French groups.

GHESKIO today: An integrated approach to HIV

From this modest beginning, the GHESKIO clinic has grown into the hub of Haiti's battle against AIDS: last year its staff of 116 provided free services for 10,000 people, including HIV testing and counseling (with about 30% testing positive), along with comprehensive STD and TB screening and care. The clinic is also a one-stop health center that offers primary care, mental health and family planning services integrated into an overall outreach program aimed at supporting families of HIV-positive individuals, who receive treatment for opportunistic infections but—except for a tiny pilot program—no HAART therapy.

However, that may soon change. With the aim of expanding the availability of HAART, GHESKIO has also begun working closely with a rural HIV clinic in Hinche called Zanmi Lasante, (Partners In Health, in Creole) led by Harvard's Paul Farmer, who is pioneering a small DOT-HAART (Directly Observed Therapy) program in people with advanced AIDS. Both groups are now collaborating with researchers from David Ho's laboratory at the Aaron Diamond AIDS Research Center in New York and Bruce Walker's group at Harvard on a five-year plan to introduce widespread HAART treatment to Haiti. The proposal has been submitted for funding, and—if backed—will begin as early as this summer. On inauguration day for the ALVAC trial, GHESKIO also announced that it was awarded a grant from UNFPA (the United Nations Population Fund) to develop a program for preventing vertical transmission of HIV using anti-retroviral therapy.

On the research side, GHESKIO maintains a strong emphasis on tropical medicine, STDs, TB, and HIV, including studies of the host factors that protect against heterosexual HIV transmission, the clinical management of HIV in children, and the prevention and treatment of diarrhea in AIDS patients. It also provides training for laboratory technicians and counselors at the Haitian Red Cross, which is in charge of all blood products in the country, with additional funding from the Fogarty International Center for Advanced Study in the Health Sciences (through Cornell).

Education, prevention and monitoring the epidemic also remain key activities at the GHESKIO clinic and at the national level, and show that prevalence rates have dropped. Last year, a survey of nearly 3000 pregnant women showed a 4.5% rate (6.7% in urban areas and 2.9% in rural regions), compared to 6.2% in

1993. An earlier study of over 4400 pregnant women from the Cité Soleil (Port-au-Prince's worst slum), showed rates of 10.3% in 1988 (*JAIDS* 3: 721-727, 1990). To date, 90% of Haitian AIDS cases are heterosexually acquired, and males and females are about equally affected; clade B predominates throughout the country. TB remains a primary risk factor for HIV disease, and STDs such as syphilis are considered co-factors. But here, too, the news is good: syphilis rates have dropped as Haitians have begun to heed a national prevention message promoting condom use and safer sex.

Building up to vaccine trials

GHESKIO's preparations for the ALVAC vaccine trial have meant tackling a variety of logistical and nuts-and-bolts issues. A crucial one has been recruiting and training local trial staff, which was done largely through GHESKIO's HVTN partner site at Vanderbilt University. Peter Wright, head of the Vanderbilt site (and of the university's Division of Pediatric Infectious Disease), has worked with Pape and his crew for seven years, and for this trial provided cross-training in areas ranging from pharmacy to data management to informed consent—resulting in a Haitian vaccine team that now includes nearly two dozen people.

Lab capacity has also been a major focus. HIV testing, viral load analysis and T-cell counts will be done on site, but for this trial the more specialized T-cell immune assays, including ELISPOT and CTL tests, will be carried out on shipped samples at the HVTN central lab in Berkeley, California (as will assays on the Brazilian and Trinidad/Tobago samples). Although there have been a few kinks in getting shipments cleared through US customs, Haiti's close proximity to the US, says Wright, is "an asset that should not be overlooked in terms of shipment of supplies and samples and the ability of investigators to get back and forth to the States."

Haiti's poor roads and telephone lines are potentially major obstacles, so to get around them the GHESKIO team relies on technology and extensive back-up systems. Staff are supplied with cell phones, while a state-of-the art computer system will track the volunteers and laboratory data—backed by technical support from a local computer firm, LOGITEK, and that rarest of miracles for Haiti: a dedicated 24-hour satellite hookup. Three power generators are in place to counter power blackouts, along with a staff "totally dedicated to the power supply," says Pape, and two companies on call around the clock to troubleshoot. A 4-wheel drive and several SUV's are available to navigate Haiti's potholes and help volunteers get to the clinic.

Establishing extensive infrastructure and support systems did cause some delays in launching the trial. Besides the factors described above, these have been attributed to a revision of the original trial protocol (to include the Brazil and Trinidad and Tobago sites), the cumbersome process of establishing cell lines from every volunteer (for use in CTL assays), changes from NIH's former HIVNET network of trial sites to the present HVTN system, and regulatory and administrative issues on both sides. Since Creole, not French, is the primary language spoken by the majority of Haitians, it has also taken time to translate all the needed documents. Haiti's shifting political climate was another contributor to delays, but Pape remained determined to secure this high-level support. "This must be Haiti's trial, not merely GHESKIO's," he says.

Yet, with the trial now underway, Cornell's Warren Johnson is optimistic that the research will continue to move forward despite the many difficulties. "In terms of sustainability, the best prognosticator is your past history," he says. "I think the fact that we have continued to develop even during the worst of years, and to work effectively, speaks for itself." If anything, he feels Haiti "has always been looked at microscopically," holding the country to a high standard of research relative to many other poor nations.

The trial volunteers

Compared to the logistical issues, working with volunteers and getting approvals for the trial have been relatively straightforward. GHESKIO's vaccine team has held nine large community forums that included virtually all the country's public and private health organizations, and ran information sessions for specialized press. These generated strong support for the vaccine trial, but also a caution against too much publicity in the general press—"because it would create an impression that we already have a vaccine," says Pape. People told us, "You should not create demand for a product you cannot provide."

The approvals process was also relatively smooth. GHESKIO has had a strong Institutional Review Board (IRB) in place since 1983, and later added a National Bioethics Committee for evaluating research activities; both approved the ALVAC trial in a record three months, says Pape. There is also a strong Community Advisory Board (CAB), whose members include two people with HIV, religious leaders (Protestant, Catholic, and Voudouist), secondary school educators, and medical students. "They wanted to make sure the vaccine does not give people AIDS, and that volunteers are not used as guinea pigs," says Pape. "There was a lot of debate, but I don't think we'll have any problem going forward."

That is being borne out by the recruitment: as of this March, over 1000 people had volunteered for the vaccine trial, some from the original low-risk cohorts established in the early 1990s. Potential volunteers are given three intensive one-hour counseling sessions, plus a follow-up test of their understanding.

The 40 final participants chosen represent a diverse pool, including people from the bidonvilles, although overall they are somewhat more educated than the typical clinic patients (due to the emphasis on selecting people who best could understood the informed consent process). They will continue to get HIV counseling and be closely monitored, and if any test HIV-positive during the trial, offered HAART therapy. "Although we did not promise any volunteer that

> *"I think the fact that we have continued to develop even during the worst of years, and to work effectively, speaks for itself."*

they would be provided with triple drug therapy if they seroconverted, we feel we have a moral responsibility to do so, and we will provide therapy to anyone who becomes infected," says Pape. The drugs will be supplied by Cornell and the New York chapter of the Haitian Medical Association Overseas. "This approach of not telling volunteers up front that they would get HAART….will encourage volunteers to continue having protected sex," he explains.

The Haitian researchers view HIV vaccine efforts as an incentive that will encourage more people to get tested, and—with the addition of antiretroviral drugs into the mix—into treatment. "It's been harder to persuade people [to get tested] without anything to offer them," Pape states frankly. "They don't see the point, and I don't blame them." And the scientists see the ALVAC trial as a building block to incorporate these efforts into a more comprehensive national AIDS program, alongside improved treatment.

Eyeing the future

Paul Farmer, leader of the pilot treatment program in Hinche, shares these views, along with the aspiration to conduct a Phase III trial in the future. He hopes the present trial can serve as a stepping stone to this goal, professing himself undaunted by the logistical challenges—although he works in a region where donkeys do better than SUVs in climbing the steep hills. "I think [a Phase III trial] is altogether feasible," says Farmer. "GHESKIO has a bigger and better infrastructure than we do, and I think even we could pull this off, especially if there's a shared commitment to treating those already sick with antiretrovirals."

Looking ahead towards that end, Pape's team is already busy screening potential future volunteers, to show that they can put together large HIV-negative cohorts. That entails expanding their high-risk cohorts (such as serodiscordant couples and commercial sex workers) and building lab capacity to perform T-cell immune assays and handle much higher sample numbers. In addition, jokes Wright, "they will have to clone several Dr. Papes."

"The major problem all international sites will face is the need to have an infrastructure in place at least one year before initiating a Phase III trial," says Pape, eyeing the next major challenge. "To me that is the most difficult thing to convey to those providing financial support." *Deye mon, genyen mon.*

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◀ **GLOBAL HEALTH FUND** *continued from 2*

UN. Support is building for a model based on GAVI (the Global Alliance for Vaccines and Immunization), which is run by a small "representative" board, a secretariat, and a larger stakeholder group.

AIDS vaccines and the Global Fund

As it now stands, the Fund would give a boost to vaccine efforts if it helps ensure increased, effective investment in health systems and better access to commodities in developing countries--outcomes that would help create a supportive environment both for HIV vaccine trials and for better use of effective vaccines once they are developed.

At present there is no commitment for a window specifically earmarked for AIDS vaccines. Yet a number of governments and public health officials have expressed support for such a window and are working to include it within the broader health fund.

In a report to be released at the UNGASS meeting, IAVI is calling for the creation of a vaccine sub-account to be used for the purchase and delivery of vaccines once they become available; no funds would be allocated until that time. According to David Gold, IAVI's Vice-President for Policy and Public Sector Support, "creation of a vaccine window would send an important message that vaccines, along with treatment, care and prevention, are crucial to overall efforts to end the epidemic. The account would also demonstrate to vaccine companies that there is a global commitment to purchase and deliver AIDS vaccines to those who need them without delay." The report, *A New Access Paradigm: Public Sector Actions to Assure Swift, Global Access to AIDS Vaccines*, also describes several key requirements for an effective fund and recommends other actions that should be taken by the public sector to ensure future access to AIDS vaccines.

Future prospects

While the Fund is likely to be a major topic of conversation among the delegates, it is not part of the official UNGASS agenda. It now appears that a new and broader working group of stakeholders will be formed to take the planning forward, up to, and beyond July's G8 meeting in Genoa. This group will include developing countries and an expanded roster of potential donors, including other OECD countries. ◆

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AIDS Vaccine Tax Legislation Proposed in the US and UK

BY CHRIS COLLINS

Legislation aimed at stimulating more private sector research on vaccines against AIDS, malaria, and tuberculosis has been introduced in the US Congress for the third consecutive year. Although it was not incorporated into the tax bill signed by President George W. Bush in May, *The Vaccines for the New Millennium Act of 2001* could still be considered later in this year's Congressional session.

On the other side of the Atlantic, vaccine research incentives are being considered by the UK.

It may seem paradoxical that financial incentives for pharmaceutical and biotech companies are being proposed at a time when the industry is being pilloried regularly in the global press for its sizable profit margins and the high prices of AIDS drugs in developing countries. Yet it is widely believed that the complex challenges of making an HIV vaccine cannot be met without greater engagement from the private sector, which has much of the expertise needed to develop and produce vaccines and shepherd them through licensing.

Although lagging industry interest in AIDS vaccine development largely reflects the daunting scientific challenges, there are also significant economic obstacles to industry participation. Research investments in vaccines for malaria, TB, and HIV are high risk and take many years to show results. Even then, the eventual market for these products is uncertain, since the vast majority of people who need these vaccines live in poor countries with (at best) limited ability to pay. It is this dilemma which has spurred the US and UK governments to look for ways of addressing the economic challenges to research and delivery of these desperately needed vaccines.

US legislation: The Vaccines for the New Millennium Act of 2001

The Vaccines for the New Millennium Act of 2001 (House of Representatives bill #1504 and Senate bill #895) was formally introduced in April and May of this year by Rep. Nancy Pelosi (D-CA) and Senator John Kerry (D-MA). Both bills are bipartisan: Rep. Jennifer Dunn (R-WA) and Senator Bill Frist (R-TN) are original co-sponsors of the legislation.

The Vaccines for the New Millennium Act of 2001 is similar to two vaccine bills introduced by Pelosi and Kerry in last year's Congressional session, when parts of the legislation came close to inclusion in the final budget deal. According to Rep. Pelosi, the legislation is intended to "leverage private sector resources and encourage the market to work more effectively" to find vaccines and microbicides urgently needed to promote international public health.

The new Pelosi-Kerry bill contains several provisions designed to accelerate private sector research and development (R&D) of microbicides for HIV and vaccines for HIV, TB, and malaria and any other infectious disease that kills over one million people per year. One key component is a 30% tax credit on company R&D expenditures for these products. Pharmaceutical companies are often criticized for dedicating a substantial share of their revenues towards advertising and profits, rather than the significant R&D expenditures they say justify high drug prices. The Pelosi-Kerry bill provides tax credits only for actual R&D investments in the targeted research during the previous tax year.

The bill also contains provisions aimed at extending these financial incentives to biotech companies, where much of the innovative private research is occurring. Many biotech companies are not yet profitable and therefore have no tax liabilities that would enable them to take advantage of traditional tax credits. The Pelosi-Kerry legislation would make the vaccine R&D credit refundable for companies that have zero income tax liability for both the current *and* previous two tax years, and gross assets of $500 million or less. For example, if an eligible smaller company spent $1 million on HIV vaccine research expenses during the tax year, it would receive a refund for 30% of this amount (or $300,000).

This refund provision is similar to an R&D incentive implemented last year in the UK that allows small and medium-sized companies to receive a cash payment for part of the value of research tax credits they accrue. The Senate version of the bill would require that refunds to biotechs be used for the targeted vaccine and microbicide research.

In addition, the Pelosi-Kerry bill would encourage larger pharmaceuticals to contract with biotech companies for targeted vaccine and microbicide research. An existing tax credit on a broad range of contracts between companies would be increased from 65% to 100% specifically for research on vaccines for HIV, TB, or malaria, or microbicides for HIV.

Accelerating access to priority vaccines

The Vaccines for the New Millennium Act of 2001 also includes several provisions intended to promote access to the targeted vaccines and microbicides once they are licensed. First, it provides a 100% tax credit on the sales value of the priority vaccines and microbicides to qualified international health organizations or governments in developing countries. This provision was based on a proposal made by former President Bill Clinton during

continued on 8 ▶

> *"The US proposal also includes provisions to promote access to vaccines and microbicides."*

◀**TAX LEGISLATION** *continued from 7*

his last State of the Union address, and is aimed at increasing the attractiveness of developing world vaccine markets to industry.

Second, the bill would create a purchase fund at the US Treasury Department, to buy the targeted vaccines and microbicides for distribution to developing countries. The fund would not receive government appropriations until a product is ready for delivery. The sales credit and purchase fund proposals are mutually reinforcing: a vaccine sales credit could bolster the effectiveness of the purchase fund by doubling the value of sales made to the fund, encouraging industry to produce more vaccines for developing countries.

Another access-oriented provision in the bill mandates that companies developing a vaccine or microbicide using the proposed R&D tax credit must present a plan for maximizing global access to the product once it is licensed. The plan would be non-binding, but it would force companies to be explicit about their efforts to achieve wide distribution of the product in developing counties, and could be a valuable tool for health advocates urging concrete action to accelerate international delivery of these essential products.

Finally, the Act expresses the "Sense of Congress" in support of tiered (differential) pricing and of publicly-supported efforts to expand vaccine manufacturing capacity.

UK proposals: Incentives for priority drugs and vaccines

When British Chancellor Gordon Brown unveiled the UK 2001 budget plan in March of this year, he announced that the government planned to create a tax credit "to stimulate research into the development of vaccines and drugs to combat malaria, TB, and those strains of AIDS/HIV prevalent in the developing world." The details of the tax credit are still under discussion, but a summary paper in the UK budget plan suggests that the credit would be valued at 50% of qualifying research and would be in addition to existing R&D tax credits.

The government also announced that it plans a "consultation" on tax incentives for donation of drugs, vaccines, and associated medical equipment to international aid organizations and public health authorities. (The US already has a drug and vaccine donation tax credit.) The UK tax incentives are part of a collection of proposals that the government says is "designed to relieve child poverty and to eradicate diseases primarily affecting developing countries."

A step in moving these proposals forward came in May, when the Performance and Innovation Unit of the UK Cabinet Office presented the government with a package of global health initiatives. Other components of the package include creation of a new Global Fund for Health to purchase existing products, an advance purchase commitment that would be a binding promise to purchase future products, such as HIV vaccines, and R&D tax credits, public-private partnerships and targeted financial support to stimulate research.

How effective are tax credits?

Would tax incentives actually accelerate research on the most urgently needed vaccines, or would they amount to another example of "corporate welfare" in the tax code? Studies of existing R&D incentives in the United States, including the Research and Experimentation Tax Credit (R&E Credit), have generated conflicting results. A summary analysis of studies on the R&E Credit published by the US General Accounting Office in May 1996 concluded that "Half [of the reviewed] studies provided estimates in support of the claim that, during the 1980s, one dollar of research credit stimulated at least one dollar of additional research spending. The estimates made in the remaining studies either do not support that claim or are

continued on 16 ▶

SURVEYING INDUSTRY PERSPECTIVES ON INCENTIVES FOR AIDS VACCINE DEVELOPMENT

Earlier this year, IAVI conducted a series of interviews with representatives of ten pharmaceutical and biotech companies and industry organizations. Participants were asked about the potential effectiveness of tax and other financial incentives to stimulate research, development, production, and delivery of HIV vaccines.

The majority of those interviewed felt that tax credits alone would have minimal impact on industry R&D decisions. But many commented that tax incentives could be effective as part of a package of interventions, especially programs to establish a paying market for vaccines. As one interviewee said, "Nothing on the push side makes a difference if you don't have a market. You need a combination of things."

Several participants thought that biotech companies were more likely than pharmaceuticals to respond to financial incentives, which would have relatively greater impact on a small company's bottom line. Since biotechs often struggle to raise sufficient capital for research, the economics of vaccine research can be as daunting as the science—so financial incentives could play an important role in generating and maintaining research projects.

For big pharma, creation of a paying market for vaccines in developing countries, along with purchase and delivery of currently available vaccines, emerged as top priorities. As one interviewee commented, "my big pharma friends say that if you want incentives to be credible, then apply them to our business today," by buying and delivering vaccines available now. But other industry representatives said that tax credits and other "push" mechanisms which subsidize R&D could help even large companies maintain existing long-term, high-risk research programs, including those for HIV, TB, and malaria vaccines.

— C.C.

Laying Groundwork For AIDS Vaccines in Developing Countries

José Esparza is Coordinator of the WHO-UNAIDS HIV Vaccine Initiative (HVI) in Geneva. A Venezuelan-born physician and Ph.D. biologist, he spent over a decade doing basic research in human virology at the Venezuelan Institute of Scientific Research in Caracas before joining the World Health Organization (WHO) in Geneva in 1986. For the past ten years Esparza has worked to promote HIV vaccine development, with an emphasis on preparing for clinical trials in developing countries. Three weeks before UNGASS, he spoke with the* IAVI Report *on a wide range of topics concerning global activities in AIDS vaccine development.

AN INTERVIEW WITH

José Esparza

What are your thoughts as you look towards UNGASS?

For UNAIDS, this is a very important event. What is important are the voices of the United Nations member states. They are the ones who have to tell the UN to do more. It is not for the UN to say this to countries. It is actually the other way around.

From my position, our role is to support the member states.

Can you give us some background about the WHO-UNAIDS HIV vaccine unit?

It is a continuation of an effort started in 1989 with the vaccine team at WHO, called the GPA (Global Program on AIDS). That year we held our first meeting, which developed the general scientific, ethical and logistical guidelines for the conduct of HIV vaccine trials in developing countries. It was a very large meeting, with all the big players from industrialized and developing countries. Looking back, I see that already then we identified the key issues.

In 1996 our vaccine team moved to UNAIDS. We were there for four years. Then Drs. Gro Bruntland (Director-General of WHO) and Peter Piot (Executive Director of UNAIDS) decided to join WHO and UNAIDS to create this new initiative. They did this to take better advantage of WHO's long experience in vaccinology, and because they thought that approaches to industry would be more convincing if we came with a package of vaccines, not only HIV vaccines.

But making an HIV vaccine is not only about immunology and vaccinology. It's also about community involvement, ethics, and creating a vaccine development program within an overall prevention effort. Our joint initiative takes advantage of the expertise of both organizations.

A major focus of your unit is on helping developing countries launch national AIDS vaccine programs. How and why did you identify this as a priority?

That goes back ten years, to the time when scientists first began seeing signs of protection in monkeys given experimental HIV vaccines. A number of people approached us asking for help in developing sites where these vaccines could move into efficacy trials. It was evident for epidemiological reasons that some trials would have to be done in developing countries.

So in 1990 and 1991, we assessed 15 countries on different continents, to identify those where vaccine trials could best be conducted. We presented this information to our vaccine advisory committee, and they recommended that we initiate activities in four countries: Brazil, Thailand, Uganda, and Rwanda. In 1992 and 1993, these four countries developed national AIDS vaccine plans.

The development of the plans was actually more important than the plans themselves. That's because they were created through a series of workshops and meetings that raised awareness in the community and among politicians, media and scientists. And they required a process of consensus building.

What is written down in these plans?

A national plan states the country's policy on HIV vaccines at the highest possible level and spells out the mechanisms for review, approval and monitoring of clinical trials. That's very important, because a big problem with initiating these trials in many countries is that nobody knows how to do them—who should give authorization, how protocols should be reviewed, and so on.

These plans also make recommendations for the conduct of preparatory research needed before launching a trial, including virology, epidemiology, cohort development and social and behavioral research. And they cover supportive activities like data management, public information, and communication.

Through these first national plans we also developed a number of cohorts in those countries. One of them, in Bangkok, is in use in the ongoing Phase III trials in Thailand.

So we actually created the beginnings of a vaccine culture in these countries. It was a long and painful process. But it brought results: a majority of the trials that have been done in developing countries so far were conducted in those countries, except for Rwanda, which was lost in the terrible war.

continued on 10 ▶

◀ESPARZA INTERVIEW *continued from 9*

> "Coordination is something that everybody wants. But nobody likes to be coordinated."

Are you involved with other countries in preparing national plans?

We are now going through this process in several countries. Last January, Nigeria held a workshop to begin creating a national plan. They now have a draft, which has to be discussed and digested. We did the same in the Ivory Coast in April, together with the US CDC (Centers for Disease Control, US), Ministry of Health and the French ANRS (l'Agence National de Recherches sur le SIDA). Tanzania will hold a workshop at the end of July, and Zambia is also interested in a plan.

Speaking of coordination, how do the national plans usually approach this?

Coordination is something that everybody wants. But nobody likes to be coordinated. That's a problem.

We don't see coordination as somebody telling everyone else what to do. National plans are essentially mechanisms for the different agencies to share information on what they are doing, so that they don't step on each other's toes.

For example, Tanzanian scientists have been working with scientists from Germany, Sweden, the US, the European Community. Through the years, they have built a very substantial infrastructure. But next month's meeting is the first time that the different international donors come together to present what they are doing and see how they can work together.

Can you tell us about the African AIDS Vaccine Initiative?

It began with a meeting we convened together with SADC (Southern African Development Community). The seven SADC countries, instigated by the regional director of WHO in Africa, Dr. Samba, wanted to discuss ways of coordinating their efforts on HIV vaccines. We were planning a similar meeting. So we joined up.

The meeting in Nairobi, in June 2000, brought together 40 African scientists from different disciplines—virologists, ethicists, epidemiologists, and public health people—to discuss what could be done to accelerate vaccine development for Africa. The participants signed a document called The Nairobi Declaration. It is a political document, and the scientists began pushing it in different regional forums, saying that these ideas should be implemented.

Afterwards the potential leaders came to Geneva and spent several days discussing it and brainstorming how to turn the intentions of the Nairobi Declaration into something tangible. We discussed many possibilities, from the creation of an African vaccine institute to simply a network of people that would exchange information. William Makgoba (president of South Africa's Medical Research Council) came up with the idea of an African AIDS vaccine program.

A steering committee was formed. Then they established five working groups: clinical and laboratory science; population studies, which includes epidemiology and social and behavioral research; ethics, law and human rights; advocacy and resource mobilization; and national and strategic planning. WHO and UNAIDS furnished US$ 1 million in seed money for the first year, to jumpstart the program.

Since then, several important political bodies in Africa have endorsed the program. And something very interesting: the 15 countries of the West African Health Organization each pledged $50,000 from their own funds, to create a vaccine development fund for West Africa. For me, it is a very, very important gesture that they put in their own resources. It says that research on AIDS vaccines is a high priority for the countries. I would like to see the African Development Bank and other African countries contribute, too.

How far along is the planning at this point?

They have what I would say is a very credible plan for the first year. It's not extremely ambitious, but it's a good start. They developed a set of activities and are now ready to invite international collaboration. They didn't want to do that until they had something concrete. That's because last year, when some African colleagues presented the idea for the first time to our international group in Geneva, the reception was very poor. People said, you don't have a specific plan; what are you proposing to do? So they learned that to have credibility, they needed a well-developed plan.

Their proposals will be presented to the international community at a meeting called the Forum of the African AIDS Vaccine Programme, planned for late this November in Capetown.

What types of activities are in the cards?

A high priority for the first year is that each of the five working groups will do an inventory of resources and needs in key countries. There are also training activities in the different areas, and funding for some preparatory social and behavioral research along the lines of what's included in the national vaccine plans. They decided *not* to get involved in cohort development—they don't have the resources for that.

The basic idea of the program is really a network of scientists. Eventually, they will move to developing local reference centers in different areas, for ethics, epidemiology, data management, laboratory issues, etc.

The plan for year one does not specifically mention clinical trials. The focus is on activities that will support any organization or country doing vaccine trials in Africa—what I'd call pre-

trial infrastructure: advocacy, including education of the media, and strengthening laboratories for trials.

You've described an example of countries trying to pull together and accelerate their collective efforts. Are there areas where you see a lack of cooperation that impedes progress?

Of course, there are some. One thing is worrying me a lot these days. I am very concerned about the danger that countries are developing their own "national vaccines"—the South African vaccine; the Chinese vaccine; the Indian vaccine.

I perfectly understand the political drive for this. I mean, South Africa would not embark on all they are doing on HIV vaccines—which is an enormous amount, and a big investment from their government—if they didn't feel that they *must* develop a vaccine for themselves; that if they don't do it, nobody else will.

But it will be a very sad outcome if we have, for example, a subtype C vaccine from India but don't know if it can be used in other parts of the world, which also have subtype C strains. It is very important not to isolate and compartmentalize those national efforts. We need to bring them together, share reagents, and compare immunogenicity of candidate vaccines that have been developed in India against subtype C, with those being developed in South Africa with subtype C, or in China with subtype C.

So networks can be very important, not only from the scientific point of view, but from the strategic point of view.

A few years ago, UNAIDS developed a set of ethics guidelines for HIV vaccine trials in developing countries. How are they working out?

I recently returned from South Africa. They are using the document there as a basis to develop their own ethical guidelines for vaccine trials. This is precisely what we wanted, and what the guidelines recommend. What we provided was a procedural document that people could use to conduct their own discussion, not a recipe for all countries.

Another interesting development is that in June a UNAIDS team, with two Thai counterparts, will travel to Bangkok to do an ethics assessment of the VaxGen Phase III trial. The principal investigator there requested this assistance, asking us to look at what they are doing, tell them what we think and make suggestions for improvements. This was also recommended in our guidelines — that clinical trials be monitored to ensure that ethical aspects of the trial are being respected.

I think the guidelines are helping to dispel the idea some people still have, that ethics is an obstacle to vaccine development. I always say that, just as immunology is not an obstacle for HIV vaccine development, ethics is not an obstacle, either. You just have to identify the issues, solve them as well as you can, and move on.

Is the ground shifting in terms of providing anti-retroviral therapy to people who become infected in the course of vaccine trials?

When the guidelines came out, some people said it was enough to provide the currently available level of care. We defended the position of providing the highest attainable level of care in the country, and that is how the guidelines read.

This issue is very controversial, because the Helsinki Declaration talks of the best proven therapy But 'best' where? In the country where the trial is taking place, or anywhere in the world? This lack of precision is what has led to so many fights and letters to journals.

We aimed for the highest attainable level of care, and for helping countries identify what that level is. And that is a moving target. Two or three years ago, people proposed giving therapy right after seroconversion—hit early, hit hard. Today, the recommendation is to wait. And the cost of antiretroviral therapy is decreasing. So the attainable level may be different.

A few years ago, French President Jacques Chirac proposed a therapeutic solidarity fund. I just saw him on TV, saying that everyone called him crazy for that. They said it was completely unrealistic. Now it's what the whole world is after.

This was the only ethical proposal, I mean, we cannot accept the status quo, that people in developing countries have no access to even a basic level of treatment.

Switching subjects again, you are heavily involved in a study to estimate demand for HIV vaccines. Can you tell us about it?

The study is intended to help to plan for access to future HIV vaccines, and is a collaboration with IAVI.

One goal is to identify policy issues that will guide the introduction and use of future HIV vaccines in countries. When I say policy issues, I mean questions like what a country's position will be if a vaccine is only 40% or 50% effective. Would they introduce it into their national strategy for AIDS prevention and control? Then there are questions about *how* countries would introduce it. Would they target specific populations? How will they make sure that use of an HIV vaccine doesn't interfere with other preventive interventions?

We also want to make estimates on the size of the target population for a given vaccine, based on these potential policy decisions, and figure out how much vaccine would actually be needed.

How are you going about this?

continued on 12 ▶

◀**ESPARZA INTERVIEW** *continued from 11*

We are holding a series of regional workshops to discuss these issues, focusing on three hypothetical scenarios: one with a vaccine showing 30-40% efficacy; one with 90% efficacy, and an intermediate scenario, around 60%. We recently met in Brazil, and I'm on my way to Korea to meet with people from Asia and the Pacific. Later in June we'll have workshops for Africa and for Europe, the US and other industrialized countries.

The Brazil workshop had 25 people, including policy makers, health ministry people, community representatives, people with experience funding public health programs, or in immunization programs. These workshops are not quantitative. They are qualitative workshops.

What were some of the responses at the Brazil meeting?

Participants had a very clear opinion that even a relatively low efficacy vaccine should be introduced in national programs—as a complement to other types of prevention, not a replacement. And they were clear that it should be targeted to high-risk groups.

But there was some concern. People saw a danger. Their message was, if we were to use this vaccine, we would have to increase our prevention efforts. So the overall prevention effort may not be cheaper, although hopefully it would be more effective.

We also learned that people were relatively comfortable making a recommendation for both low- and high–efficacy vaccines. But for intermediate vaccines, they couldn't decide. They said we need more data. We would need to have mathematical models to be able to decide.

What variations and differences of opinion do you expect among the different regions of the world?

One difference will probably concern the low efficacy vaccines, which would most likely be targeted to specific populations. People have already modeled the potential use of low-efficacy vaccines. For example, Roy Anderson has concluded that a vaccine with an efficacy around 40% may have a positive effect in populations that meet two conditions: HIV incidence is more than 1—1.5%, and that preventive interventions are not readily available.

Other modelers, like Sally Blower (Univeristy of California) have proposed that if you use a low-efficacy vaccine in San Francisco, where she modeled, it could have a deleterious effect; it could in fact lead to increased incidence, because of the potential for interfering with other types of preventives. We are working in collaboration with people from Emory University and with CDC, modeling vaccine use for public health purposes.

The different economic realities and levels of the epidemic will also play a role. For instance, in Europe and the US, we may find a situation that doesn't exist elsewhere: competition between the public and private demand. There could be individuals willing to pay a thousand dollars for a vaccine. For public health purposes, the vaccine cannot cost that much. How will you deal with this?

What will you know at the end of the workshop series?

We will have a very rich list of policy issues to help us plan vaccination strategies and identify gaps we need to fill by going back and doing targeted research.

Using feedback from the workshops on how different countries are likely to use vaccines of low, medium and high efficacy, we will also try to estimate the size of the target population for these vaccines. This is not so easy, but fortunately we have use of a UNAIDS database on potential risk populations in different countries. This provides a good starting point to estimate the size of the population that would benefit from an HIV vaccine.

Then we need to estimate how many of these people would actually receive a vaccine. This depends on the accessibility of the target population and, of those who are accessible, how many will be willing to receive, say, three vaccine doses. We went through an intensive exercise on this, although we had to make some guesses.

But now we are getting numbers.

And what will the numbers tell you?

Based on the preliminary information we have so far, the numbers look manageable.

Sometimes I feel like I did early in the epidemic, when we used to talk with Jonathan Mann about not knowing how many people in the world were infected. Was it 100 million, or five million, or one million? We had no idea.

Today, when we talk about the use of a vaccine in the future, we really don't have a handle on how many doses we are talking about. I have seen calculations that go up to three billion, which is absolutely impossible; there is no production capacity in the world for that. With reasonable estimates in hand, countries can plan public health programs, industry can plan manufacturing facilities and financing institutions like the World Bank can calculate the financial need.

We will also have some basis to start discussing serious business with industry and with the financial institutions, so that when a vaccine is developed, we can move as quickly as possible to delivery. That's why I'm so excited to work with IAVI on this. And we can tell Kofi Annan and others: from this war chest of several billion dollars, we will need this much for HIV vaccines. ◆

A New Research Center Tackles AIDS Vaccines

AN INTERVIEW WITH Gary Nabel

In April, 1999, Gary Nabel became the first director of the new Vaccine Research Center (VRC) at the National Institutes of Health in Bethesda, Maryland. Prior to taking this position, he was director of the Center for Gene Therapy and a Howard Hughes Medical Institute investigator at the University of Michigan in Ann Arbor. Nabel is well-known for his work on HIV, cancer, and Ebola virus, and for his gene therapy clinical studies. Here he talks with the IAVI Report about the research program at the recently opened VRC, which will work primarily on AIDS vaccine development, and about the scientific challenges facing the field.

How far along is the VRC in getting up and running?

We began our building and recruitment of staff two years ago, and are now at the point where we're beginning to gel as a center. Hiring is complete and our investigators are moving in and setting up their laboratories. Four labs are running, and we hope that all the investigators will be here in July—about ten tenure-track scientists and some high-level professional staff to run our core facilities.

What will be the Center's main focus?

We're directing most of our efforts at the early stages of AIDS vaccine development—translating concepts from the laboratory into the clinic, and testing approaches and methodologies for identifying promising leads and advancing good candidates. We have brought in people from areas as basic as X-ray crystallography, to work on the structure of HIV envelope, and from virology, immunology, clinical production and clinical trials.

We view our mandate as being, first of all, to address the major scientific problems before us. And second, to use that knowledge to expand the pipeline of candidates into trial.

What "value added" does the VRC bring to the overall AIDS vaccine effort?

The key thing is critical mass. In putting this building together literally from the ground up, we've had the luxury of starting with a blank slate and asking what we want to build and how to assemble a group to accomplish it. Although we're not a large center—altogether we will have between 100 and 125 scientists—it is sufficient for getting things done, without being so big as to lose the personal connections that help people work well together.

All the investigators here have a common purpose. And we hope that having them under one roof will catalyze progress in difficult areas.

What are the key scientific problems you're working on here?

I think the rate-limiting step for a highly successful AIDS vaccine will be the development of broadly neutralizing antibodies. Scientifically that's the major question we would like to impact here.

Most people in the field believe that cytotoxic T-cells will be important in containing the virus, and that we should be able to develop vaccines which elicit CTL responses and confer some degree of protection. How well they work is likely to depend on how long we can sustain active responses and how quickly we can recall them. I think we can do more to help that process along, but my guess is that we'll hit a wall in terms of how effective this approach will be.

The virus envelope is a very formidable target. It's been possible to generate neutralizing antibodies to specific strains of virus from specific laboratory isolates. But it's been quite uncommon to have broad antibody responses that neutralize many strains within a clade, even less so multiple clades. That's the key issue we need to address.

Another challenge is that, behind every successful vaccine is an example of immunity in humans or a good animal model to guide our efforts. With HIV we have exactly the opposite—the virus has figured out pretty successfully how to evade immune detection. We have to get at the heart of how the virus accomplishes this and try to build the immune correlates that will help us develop an effective vaccine.

How will you approach the neutralizing antibody problem?

We will come at it from several directions, starting with a structure-based approach. Joining us in the Center are two scientists who were major movers in solving the crystal structure of gp120 — Peter Kwong and Rich Wyatt. Together with Wayne Hendrickson and Joe Sodroski, they published the first structure of gp120 complexed with CD4 and a monoclonal antibody. We're hoping to identify structure-based modifications of gp120 that might allow us to present otherwise cryptic epitopes or hidden structures which could be useful immunogens for eliciting broadly neutralizing antibodies.

It may or may not be possible to develop antibodies of this sort. But we need an answer to that question, one way or another.

We will also approach the problem genetically by making a series of mutants, again based on what we know about the structure and function of gp120 and on gp41, from the Kim and Wiley laboratories.

The real issue—like for other challenging infec-

continued on 14 ▶

◀**NABEL INTERVIEW** *continued from 13*

tious diseases nowadays—is that the HIV envelope is a moving target. Literally moving, because it's conformationally active and never allows you to have a static view of structures you'd like to neutralize. And genetically moving, because it's constantly evolving new sequences.

You're also making lots of vaccine constructs. Can you tell us about them?

My laboratory has been generating vaccine candidates based on DNA and on viral vectors, primarily adenovirus, to test different vaccine concepts. The approach is to hypothesize what components are needed for a vaccine and then develop candidates to test that concept. We're looking at combinations of immunogens that generate cytolytic T-cell responses, particularly to the internal proteins of the virus—mostly Gag and the *pol* gene products—and to Nef. We also think it's important to generate CTL responses to envelope. In terms of antibody, obviously the exposed proteins would be the ones we target, primarily envelope.

We now have prototypic DNAs encoding all these gene products. We'll also take the same inserts used in the DNA and introduce them into viral vectors.

You recently received approval for your first Phase I trial. Can you tell us about it?

The product is a *gag-pol* fusion, engineered to express the *pol*-encoded proteins at higher levels than in wild-type HIV. It's part of our strategy to try to enhance the breadth of the immune response.

This is a prototypic construct. I don't expect it will be the only immunogen in the end. But it's an important step because it allows us to develop our methodology for starting with a construct in the lab and moving it into the clinic. We should now be able to introduce new candidates more rapidly.

What are the concrete plans for the trial?

Once we have screened all the patients, which usually takes about two months, we'll start the trial. It's a standard Phase I study, with seven people per dose and a dose escalation—altogether 20 to 25 patients.

The trial will be done here at the NIH clinical center. We'd like to use these early trials to collect safety and immunogenicity data and begin looking at strategies for enhancing immune responses. When we identify the more promising approaches, those candidates will be fed into the HVTN pipeline and then progress to Phase II and III trials—a passing of the baton to the larger networks.

How do you prioritize which candidates should move into Phase I trials?

In our preclinical studies, we look for immunogens that give the broadest and most potent responses. For CTLs, we start in mice. For antibody responses we look for the highest titers and best neutralization, primarily in guinea pig and sometimes rabbit.

Our other criterion is the response in non-human primates. We are trying to move directly from small animal models into Phase I human studies, at the same time that we move these prototypes into monkeys. In the primate models, we can again get readouts of immunogenicity. More important, we can look at how those vaccine candidates respond to a viral challenge.

So non-human primate studies are not a gatekeeper for human trials?

That's correct. If there was less urgency, we might take the more traditional path of progressing from small animals to non-human primates to human. Also, we are still not convinced that the monkey model is exactly predictive of what will happen in people. The Indian rhesus and some other macaques are very good models, but there are differences among the animals and between HIV and the viruses that infect monkeys. At the end of the day, it's the Phase III trial that will tell us whether the vaccine works. We need to get to that endpoint sooner rather than later.

Do you have enough data to say whether results in small animals predict outcomes in monkeys and in humans?

We can't yet say with confidence. But there are trends emerging. Roughly speaking, an immunogen that works really well in mice also works in primates, and a little less well in humans. In other words, many vaccine candidates show roughly similar results in the different systems, but with a decreasing level of performance as you move up the evolutionary tree.

What can researchers do to cope with the shortage of Indian rhesus macaques? How can they help turn things around?

This is really is a critical issue, and many of us are trying to approach it in different ways. When you have a problem as rate-limiting and important as this, you can't rely on any single solution.

Clearly, we need to increase breeding supply. That takes great discipline, because we also have urgent experiments to be done. So we as a field have to look carefully at the experiments we do, and

use the available animals in the most intelligent way. Making matters worse is that demands for these animals come not only from the research community, but also from the pharmaceutical industry. And we are not in a position to control them.

We also need to look for alternative sources of animals and for solutions we might not otherwise find ideal — like doing experiments abroad in countries with animal colonies, but where we will need to invest in infrastructure so the experiments can be done with state-of-the-art analysis.

The other important avenue, which I think can move forward relatively quickly, is to look at other monkey species or strains. We've been very high on the Indian rhesus macaque because there are so many specific reagents for looking at their immune responses. But there's really no reason we can't do the same in Chinese macaques or cynomolgus macaques. It may be easier to make new reagents than to wait for until enough Indian macaques have been bred.

Is the VRC working in this area?

Yes. Norm Letvin is our director for primate studies. Together with John Mascola, our deputy director, he has been involved in looking globally at the broader questions, not just for the VRC, but for the whole field.

The VRC alone cannot solve this problem. But we can help develop some reagents and make them broadly available. We're also looking at the Chinese rhesus and cyno models, and at different virus challenge stocks and how they behave.

There may be a silver lining to this cloud. There's some suggestion from preliminary data, not yet published but being discussed at meetings, that viral loads in Chinese rhesus monkeys better approximate viral loads seen in humans, both at the peak of infection and at steady state. We'll know within six months whether this is more widely true. If so, it might be a more realistic model than Indian rhesus macaques.

We shouldn't underestimate how much work it would be to sequence the MHC region of the Chinese macaque and to develop reagents like tetramers. But it can be done.

How does your adenovirus approach compare with what Merck is doing?

The adenovirus we use is a very potent immunogen. As a vector it does very well in eliciting both cell-mediated immune responses and very high titer antibody responses, particularly when combined with DNA.

We became very impressed with the power of this approach when we began working on Ebola virus vaccines several years ago. In a rodent model, the DNA vaccines alone worked perfectly fine to protect animals against lethal challenge. But when we applied our correlates of immunity from these models to monkeys, the same DNA vectors couldn't come close to inducing those responses. We then found that adenovirus was very effective in achieving these correlates of immunity, and it proved its efficacy in a monkey challenge model. So we're using it again.

In terms of what HIV antigens you put into those vectors, or the different prime boost strategies—there are many possible directions to go. Merck is moving its own set of genes forward. Many of their products appear to be directed towards generating CTL responses against internal proteins. We agree that this is a good idea. But we also want to make sure that envelope is well-represented. The issue of targeting any vulnerable structures on envelope is very high on our agenda.

I liken our efforts with adenovirus to the situation when different groups were trying to develop anti-retrovirals. Many people developed anti-retrovirals against reverse transcriptase, and many products came forward. There was no way to know ahead of time which ones would work best. Clearly, the only way to find out was by testing them in the clinic. So I suspect at the end of the day, that's how we'll work with vaccines. As the virus has taught us, we're best served by having diverse approaches.

How has your work in Ebola influenced your thinking about the approach to making an AIDS vaccine?

Ebola has many parallels to HIV infection. When we first started working on it, it wasn't at all clear you could generate immunity to the virus, or what those correlates of immunity were. But we've developed approaches that generate immune responses which seem to be protective, and which allow us to establish correlates of immunity in animal models that we now apply to the human situation— much as we're trying to do this for HIV.

And, as we just discussed, with Ebola we also identified some very promising technology platforms, and some important concepts in terms of how to move reagents out of the laboratory into the clinic. We're using those concepts in our HIV work.

How far along are the Ebola candidates?

We are in the process of making clinical-grade material and beginning the regulatory process. We would love to begin Phase I studies of Ebola on DNA and adenoviral candidates as well.

What do you see as the main bottlenecks in moving vaccine candidates into the clinic?

The bottlenecks are highly dependent on what candidates you're talking about. DNAs are now among the easiest to get into the clinic. But even then, there are a limited number of facilities that can make GMP-grade DNA. It's even more challenging to produce viral vaccines.

Beyond the capacity to manufacture vaccines,

continued on 16 ▶

> *"We are trying to move directly from small animal models into Phase I human trials and monkey studies."*

◀**NABEL INTERVIEW** *continued from 15*

the issue of what packaging cell lines are safe and can be used to produce vaccines is a critical one. For many years, we've been tied to primary cell lines for producing vaccines. We, the FDA and the whole field are trying to develop an approach that will make it possible to use permanent cell lines, by addressing the various questions this raises.

The recent report by AVAC, which reviewed the state of the US AIDS vaccine effort [see Vaccine Briefs, p.20], said that the VRC may be somewhat underfunded.

At this point, since we're not fully staffed, I don't think so. When our activities grow and we have all the scientists on board, then yes, we may have increased needs. But I'm quite comfortable that the NIH leadership knows what those needs are and will keep ahead of the curve. Already we've had tremendous recognition by NIH, not only in terms of research support, but in thinking about new ways of giving that support. There is not another organization on campus like the VRC, where the entire building is dedicated to a single purpose like our mission of developing an AIDS vaccine.

We've also had recognition from the leadership that we might need new types of infrastructure. For example, another major impediment to making new vaccines is being able to produce clinical lots. We don't have that capacity here, but NIH is supporting the construction of a pilot plant with five or six production rooms, which is now going up in Frederick, Maryland. It should come on line in about three years.

This tells me that not only are the resources there, but so is the vision, commitment and dedication. So I'm not worried about funding.

Now I'll ask our usual closing question: How long do you think it will be until there's an AIDS vaccine? It's perhaps especially fitting here, since the VRC was originally conceived as part of President Clinton's declared goal of an AIDS vaccine within 10 years.

My view of the timeframe suggested by our former president is that it was a very useful device to mobilize the field. There have been very few, if any, vaccines ever developed in that timeframe. But this is a very special circumstance and we should leave no stone unturned in terms of getting to that end.

I think it's conceivable that there could be a vaccine in that timeframe. But we would have to be extraordinarily lucky, considering that it will take another at least two years to get good candidates to the point of entering Phase III trials, which then take several years to perform.

But I do think we should know within that timeframe whether the AIDS pandemic can be contained through vaccination. I'm very hopeful that vaccination will be the answer and that within the ten year period we will see the end and know that the goal is achievable. Whether that end will then take another two years or five years, I don't know. That's what I think we need to aim towards in the VRC and in every other laboratory that's trying to solve the problem. ◆

◀**TAX LEGISLATION** *continued from 8*

inconclusive." An analysis of industrial tax policy published in 1997 by the National Academy Press determined that the R&E Credit "has had a modest impact in stimulating private R&D investment."

But while existing incentives may have affected private sector R&D spending in general, they have been far less successful at stimulating research on the products needed most in developing countries. This is most likely because credits such as the R&E can be used to subsidize a broad range of research, from anti-depressant or cardiovascular drugs for Europe and the US, to malaria vaccines for developing countries. It is no wonder that products for rich countries consistently win out when corporate priorities are set.

To create incentives for developing microbicides and vaccines against the most deadly infectious diseases, the credit proposed by Pelosi and Kerry is both more generous and more targeted than the existing R&E Credit. So will it work better? That is difficult to predict in advance, especially since in practice, its effects would probably vary for different products and types of companies. But some positive signs come from interviews with industry representatives (see sidebar, page 8), who indicated that tax credits *could* provide some incentive for vaccine research—if they are packaged with other interventions, particularly credible purchase capacity.

Besides calling for tax credits, the legislation also proposes careful evaluation of their effectiveness by directing the US Institute of Medicine to study this question and report its findings to Congress within five years of the bill's passage.

Prospects for adoption of vaccine incentive legislation

Growing international momentum to address AIDS and other infectious diseases may boost the chances for passage of key components of the US and UK proposals. One scenario is that purchase fund commitments from the US, France, the UK, and international forums, including the UN Special Session on AIDS, could lead to the creation of a multipurpose global fund for drugs and for infrastructure to address infectious diseases. The vaccine purchase fund envisioned in the Pelosi-Kerry bill could then become one sub-account within a larger purchase fund. Following the lead of the UK, governments should also make "binding promises" to provide necessary monies for vaccine and microbicide purchase when these products become available.

The international community is finally recognizing the moral and economic imperative to deliver the benefits of existing medical technology more equitably to people around the world. The new US and UK proposals are attempts to make accelerated development and delivery of future technologies part of these expanded international efforts against infectious diseases. ◆

Chris Collins is a consultant with Progressive Health Partners and President of the Board of the AIDS Vaccine Advocacy Coalition (AVAC). Previously, he was on the staff of Rep. Nancy Pelosi and helped develop an earlier version of the vaccine incentive legislation described here.

◀ **MUCOSAL STUDIES** *continued from 1*

assays are beginning to replace the invasive, variable sampling methods that have been a major bottleneck, as several speakers described at the recent AIDS vaccines conference in Keystone ("*AIDS Vaccines in the New Millennium*," 28 March - 3 April). A number of labs are comparing different immunization routes for their ability to induce mucosal responses, and there are even a few mucosal vaccine candidates in the pipeline. And overall, more and more animal studies are using mucosal (rather than intravenous) challenges. Taken together, these leads could help move mucosal research closer to the mainstream of AIDS vaccine work.

"More people are working in mucosal immunology," says George Lewis, director of vaccine development at the Institute of Human Virology (Baltimore). "The science that's getting done there is better than it used to be. We're seeing a shift in momentum," he adds, in a field that doesn't change gears easily or quickly.

Mucosal responses and protection: making the link

The first evidence for an association between between mucosal responses and protection in humans came from studies on the immune systems of women who were highly exposed to HIV, either through sex work or through an infected stable sex partner, but remained seronegative (exposed seronegatives, or ESN). Rupert Kaul (Oxford University) and colleagues and Mario Clerici's lab (University of Milan) each found that a high proportion of these women had secretory IgA in their genital secretions, compared to HIV-positive women or low risk controls. Since then, other groups have made similar observations in some, but not all, ESN cohorts. In a separate study by the Kenyan research group, many ESNs also showed HIV-specific CD8 T-cells in their genital tracts, and the ratio of mucosal to blood CTLs was generally high; HIV-infected women tended to show the reverse ratio.

In Keystone, Sarah Rowland-Jones (Oxford University) extended these findings, reporting that CD8 responses in ESN women who have remained seronegative for at least three years tended to have higher HIV-specific CD8 T-cell levels in the blood than ESN women whose period of exposure was less than three years. The team has not yet looked at these responses in the mucosa, but they now plan to follow a group of these sex workers prospectively and look at the effects of a break from sex work on both systemic and mucosal responses, as well as on HIV status.

Mucosal versus systemic immunization in macaques

At Keystone, Jay Berzofsky (National Cancer Institute, Bethesda) caused a buzz with data from a small study showing that mucosal, but not systemic, immunization protected macaques against an SIV challenge—results that mimic his lab's earlier findings in mice. In this study, macaques were immunized intrarectally (ir) or subcutaneously (sc) with a peptide vaccine containing two epitopes from SIV-Gag and one from SIV-Pol.

Berzofsky reviewed data from three animals immunized ir, four sc and two control animals that were successfully infected via ir challenge with pathogenic SHIV-ku and then monitored for 200 days. (One control and one animal from the ir group did not become infected.) All infected animals showed similar viral peaks shortly after challenge. But following this peak, the three IR-immunized animals brought their viral loads down to undetectable levels and maintained high CD4 counts out to 200 days post-infection. In contrast, the four sc-immunized animals had significant viral loads and CD4 T-cell count declines. All seven immunized animals showed some degree of protection in comparison with the two controls, which had the most pronounced CD4 T-cell depletion.

At 200 days, animals were sacrificed, autopsied, and evaluated for HIV levels in the colon and jejunum. Both these organs are lined with gut-associated lymphoid tissue (GALT) where, early in infection, HIV establishes a large pool of replicating virus which then seeds the bloodstream. Berzofsky and colleagues hypothesized that mucosal immunization could enhance protection by boosting responses in these tissues, thereby reducing viral load at the "supply source."

Their results were consistent with this notion: little or no HIV was seen in the colon and jejunum of ir-immunized macaques, while control and sc-immunized animals showed 10-100 times more virus. Most important, the three infected IR-immunized animals had significantly higher levels of HIV-specific CTLs in their colon than the sc-immunized animals, suggesting that CTL played a key role in controlling viral replication in these tissues. The data also agree with Berzofsky's earlier studies in mice showing a clear link between mucosal vaccination, the generation of mucosal CTLs, and protection against subsequent mucosal challenge. In addition, Michael Murphey-Corb's group at the University of Pittsburgh found a correlation between strong anti-SIV responses in the gut of macaques and protection against subsequent challenge with a heterologous primary isolate (SHIV/Delta-B670). The latest work from Berzofsky is the first to correlate a mucosal (vs. systemic) route of immunization with both improved local responses and improved protection in primates.

"It's an important result," says Paul Johnson (New England Regional Primate Research Center, Cambridge), who also presented new data on induction of mucosal responses at the conference (see below). "It suggests that it may be better to induce mucosal versus systemic responses." For Berzofsky, the results are a step in the

continued on 18 ▶

◀ **MUCOSAL STUDIES** *continued from 17*

> "For non-replicating antigens, the route of immunization may be especially important."

direction of complete protection. "Our hope is that with a stronger mucosal response we might do even better," he said at Keystone.

Can systemic immunization induce sufficient mucosal responses?

Berzofsky's study also raises a key question for the field: is mucosal immunization the best way to stimulate mucosal responses, as his data suggests, or is systemic immunization sufficient, at least with some vaccines?

Julie McElrath (University of Washington, Seattle) has conducted one of the few studies of human mucosal responses to HIV vaccines. Last year at the World AIDS Conference in Durban, her colleague Luwy Musey reported that systemic immunization with an HIV-canarypox vaccine (ALVAC vCP205) induced cervical or rectal CTLs in 4 of 7 tested volunteers who also had blood CTLs. Blood and mucosal CTL had the same epitope specificities, suggesting that systemic immunization induced responses in both compartments.

Based on these observations, and lack of evidence to the contrary, McElrath believes that systemic immunization will induce sufficient protection in the blood and at the mucosal sites. She believes that most CTLs in the blood are en route to the site of infection—and that, regardless of immunization route, a large proportion of T-cells in vaccinees who subsequently become infected will home to the genital mucosa. "I am not yet convinced that we have data in humans saying we have to target mucosa,' she says. "I'm sure it doesn't hurt, but I don't think we need to do it."

Other researchers point to findings that the numbers and types of immune cells can differ dramatically in the systemic versus mucosal compartments, which operate largely independently of one another. While systemic responses can correlate with mucosal responses, there are also hints from the Kenyan ESNs and elsewhere that anti-HIV responses differ between the two compartments. For example, Deb Anderson of Harvard University (Cambridge) has studied CTL in the blood and semen of HIV-infected men and ALVAC trial volunteers, and found differences in cell-mediated responses in the two immune compartments. "This suggests that the peripheral immune response isn't reflective of the genital tract," she says.

Do these differences mean that systemic vaccination will leave mucosal sites unprotected—or is exchange between the two compartments enough? Looking at other diseases, it's known that systemic vaccines against pertussis and influenza (both of which infect mucosal tissue) induce protective mucosal antibodies which appear to be derived from the blood. Yet conclusions drawn from vaccines for diseases that target the respiratory mucosa may be less relevant to HIV, a chronic, sexually-transmitted infection that targets immune cells. More antibody may be needed for a disease like HIV, say some researchers, who argue that until we know otherwise, it makes sense to pursue strategies which maximize responses at the site of infection.

"Nobody knows how much or what type of antibody you need in the serum or secretions to get mucosal protection from HIV," says Harvard's Marian Neutra, who is working on this problem. "The highest level of antibodies in tissues and secretions is attained when you immunize locally." At Keystone, Neutra presented recent data by colleague Pam Kozlowski comparing IgA levels induced in various mucosal tissues by a test vaccine (containing recombinant cholera toxin B) given to women via different immunization routes. The results showed large variations: high antibody levels in the rectum were seen after rectal immunization, but not when vaccines were given orally, vaginally or nasally. Vaginal and nasal immunization both induced good cervical responses.

More insight on immunization routes is coming from the work of immunologist Tom Lehner (Guy's, King's & St. Thomas' Hospital Medical Schools, London). Next year, he will launch an amfAR-funded trial of targeted iliac lymph node immunization (TILN) in men using a canarypox vaccine and gp140 boost. Lehner has pioneered TILN, which deposits vaccine in the vicinity of the local lymph nodes in the groin. In his earlier comparative studies with oral, nasal, rectal,vaginal, and systemic immunization, TILN induced the most consistent levels of mucosal IgA and IgG. These studies also suggest that the vaccine does not need to be applied at the mucosa as long as primed immune cells travel there after immunization.

Several researchers, including Tom Lehner, George Lewis and Paul Johnson, have suggested that the antigen itself may be a determining factor: perhaps a replicating vaccine vector such as live-attenuated virus or attenuated salmonella makes its way to the mucosa and induces responses at these sites, even if it is administered systemically. That's just what Johnson found when he compared immune responses in macaques immunized with live-attenuated SIV to those given a DNA-MVA vaccine: In four macaques given a live-attenuated SIV vaccine, between 36-84% of the total SIV-specific CD8 T-cells expressed alpha4beta7, the "homing" marker that identifies cells trafficking to the gut mucosa (see below). In contrast, the range in three DNA-MVA vaccinated animals was 5-6%.

For non-replicating antigens, the route of administration may be far more important, according to this line of thinking. That's why induction of mucosal responses with a peptide antigen, such as the one Berzofsky used, may require a mucosal route—otherwise these key barriers will never "see" the antigen. This could also hold true for vaccines like MVA, which have limited replicative capacity.

Homing in on new markers of mucosal protection

Until recently, all discussions of mucosal immunity have led to the same impasse: the extreme difficulty of gathering data from human subjects. Cytobrush technique, the standard assay for gathering cells from the female genital tract, gathers fewer than one million cells, and samples are easily contaminated by blood. Paul Johnson's lab has also developed a new "pinch biopsy" technique that allows for relatively atraumatic, ongoing sampling of vaginal and rectal tissue. While useful for animal models, however, this procedure is limited by huge variability within the mucosal tissue, making sampling highly non-reproducible: the composition of a biopsy sample can be dramatically different from tissue just a few millimeters away.

At least a partial solution now appears to have been found: several researchers, including Johnson, are pioneering the use of homing markers as a way of measuring mucosal responses in the blood. Well-known to basic immunologists, homing markers are cell surface molecules that indicate the destination of cells in the blood stream. One such marker is alpha4beta7, an integrin that appears on virtually all cells trafficking to the gut–making it possible to monitor these cells from blood samples rather than from the mucosa itself. Although the exact specificities of other potential markers have yet to be fully defined, these molecules could become powerful tools for applied vaccine research.

Their usefulness in the clinical assessment of vaccines will soon be put to the test. Phase I clinical trials are expected to start next year for a mucosal (oral) vaccine candidate based on attenuated Salmonella, an enteric bacteria, as a vector for HIV-DNA. The study will be carried out in the US by the IHV (George Lewis' home institute) and in Uganda as a collaboration between the IHV, the Uganda Virus Research Institute in Entebbe, and IAVI. The HIV-DNA to be incorporated into the vector is now in trials as a systemic naked DNA vaccine in Oxford and Nairobi and in an MVA viral vector, which will allow comparison of these different immunization routes.

Besides alpha4beta7, the study may also analyze CXCR3, a chemokine receptor found by Paul Johnson on a high percentage of cells trafficking to the female genital tract in macaques. Another candidate is CCR7, a marker of immune memory cells that localize in the lymph nodes. Cells without CCR7 appear to home to peripheral sites, including the mucosa. When combined with tetramer staining, these markers should allow for more precise quantitation of cells, both in blood and in the small samples obtained by cytobrush or biopsy.

Future directions

These new assays should make it easier to monitor mucosal immune responses in large-scale vaccine trials, taking the field into uncharted territory. With the exception of Sabin's oral polio vaccine and the nasal adenovirus vaccines used to protect military recruits from colds, almost all licensed human vaccines are thought to work via systemic immunization. The new possibilities in mucosal research may not change this focus—which has yielded many successful vaccines thus far—but should provide a much clearer picture of how these vaccines work at mucosal sites.

At the more basic research level, several other promising avenues of research could lead to better targeting of the mucosa. For example, efforts to fill in the picture of early events in HIV infection are pointing to steps where intervention might contain the virus locally, before it spreads through the body. Dendritic cells in the mucosa appear to ferry HIV to the local lymph nodes, and from there it quickly spreads to other sites, including the gut. Over the past year, this understanding has led to an intense focus on DC-SIGN, the receptor which plays a key role in carrying HIV to the lymph nodes; efforts to understand and inhibit this activity are ongoing.

Other efforts are focused on developing strong mucosal adjuvants. Immunologist Tom Lehner is studying 70kD heat shock protein (HSP70), which appears to upregulate expression of some protective chemokines, while Ken Rosenthal (McMasters University, Ontario) is testing CpG, an adjuvant made from fragments of synthetic bacterial DNA, which he showed can enhance genital immune responses, including antibodies and killer T-cells, in mice given an intranasal herpes vaccine. And at IHV, George Lewis and David Hone have developed an altered form of cholera toxin, one of the most widely-used mucosal adjuvants, that is considerably less toxic than the current formulation, which causes diarrhea.

Useful data on immunization routes could also come from studies that challenge monkeys in a manner more akin to the actual conditions of sexual transmission—multiple low-dose exposures over time—rather than single, high-dose i.v. challenges, says Julie McElrath. Another possible strategy is a a prime-boost local-systemic combination.

Once again, the polio vaccine story offers important lessons, says Tom Lehner, who points out that Salk and Sabin reached the same goal with two different vaccines—one systemic, the other mucosal. "In the final analysis, it may be a situation like polio, where you have two different vaccines and they both work," he says. But with a virus that has so far eluded a vaccine, it is important to look at all strategies—including mucosal immunization, he says. "HIV goes for some essential parts of the immune system. Whatever we have learned previously may not apply." ◆

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iavi International AIDS Vaccine Initiative

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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vaccine BRIEFS

GlaxoSmithKline Announces Vaccine Program

GlaxoSmithKline, the British-based pharmaceutical company and one of the world's leading vaccine makers, gave the first public presentation on its AIDS vaccine candidate at the Second International Conference on Vaccine Development and Immunotherapy in HIV (San Juan, 22-25 May). Lead scientist Gerald Voss reported on two rhesus macaque studies of its recombinant protein-based vaccine, containing the HIV Nef and Tat regulatory proteins (as a single "fusion protein" designated NefTat) along with gp120. The Nef and Tat proteins are derived from a laboratory-adapted clade B HIV isolate, the gp120 from a Dutch clade B isolate (ACH320) that is dual-tropic (able to infect T-cells via both CCR5 and CXCR4 co-receptors). The vaccine is delivered in a proprietary adjuvant developed by the former SmithKline Beecham (then called SBAS-2, now known as ASO2A), characterized by Voss as a mixture of a novel oil/water emulsion, 3D-MPL and QS21.

The first study involved six groups of four macaques each. Three groups received either all proteins, NefTat or gp120, all in AS02A. Another two groups received either all proteins or NefTat in a related adjuvant, AS06, while controls received adjuvant alone. All recipients of NefTat (in both studies) were also given SIV nef separately. Animals were immunized at months 0, 1 & 3 and then challenged intravenously one month later with SHIV89.6P. Voss reported that animals vaccinated with all proteins in ASO2A recovered CD4 T-cell counts after an initial dip and controlled viral replication out to 18 months. In contrast, three of four controls as well as all animals given gp120 or NefTat alone rapidly lost CD4 cells, developed symptoms of simian AIDS and were euthanized. The group receiving all proteins in ASO6 remained healthy, although three had persistently high viral loads. Voss reported a statistically significant difference between this group and controls in terms of CD4 count and viral load endpoints.

Attempting to confirm these results, Jonathan Heeney's group (the Biomedical Primate Research Center, Rijswijk, The Netherlands) immunized and challenged macaques (described by Voss as "genetically unrelated" to the first set of animals) on a similar schedule, using four groups of six animals each. After challenge, five of six animals receiving all three proteins showed relative preservation of CD4 cells but one animal experienced a clear decline. Control of viral load was variable and less robust than in the first experiment. Further confounding the results, none of the six control macaques experienced the "crash" in CD4 cells typically seen with SHIV89.6P challenges, and four ultimately controlled their viral loads. Overall, the study did not yield statistically significant differences in outcome between vaccinees and controls.

Voss also presented limited data on pre-and post-challenge immune responses. Neutralizing antibodies were detected only in one animal prior to challenge, indicating that they did not play a role in this model. T-helper cell proliferative responses to vaccine antigens were detected but declined post-challenge. CTLs are being investigated in ongoing experiments. Phase I human trials of the vaccine are slated to start later this year through the HIV Vaccine Trials Network (HVTN).

John Curd Moves From VaxGen to Maxygen

John G. Curd, MD, has left his position as Senior Vice President for Medical and Regulatory Affairs at VaxGen, Inc., where he oversaw clinical testing of the company's envelope-based vaccine candidate, AIDSVAX™. In that capacity he helped plan and launch the world's first Phase III AIDS vaccine trials, now ongoing in North America, Europe, and Thailand and collectively involving about 7500 high-risk volunteers. The search for his replacement is underway at VaxGen.

On 1 May 2001, Curd assumed the newly-created position of Senior Vice President, Clinical Development at Maxygen, Inc., a biotechnology company specializing in the optimization of genes and proteins for commercial uses, including therapeutics and vaccines. The company recently announced the start of an HIV vaccine research program in partnership with IAVI and DBLV LLC, an entity established and financially supported by the Rockefeller Foundation. Curd will be responsible for overseeing the clinical development of Maxygen's lead products.

Six Years and Counting: AIDS Vaccine Advocacy Coalition Releases New Report

Every year since 1997, when then-US President Bill Clinton challenged the world to develop an AIDS vaccine within a decade, the Washington, DC-based AIDS Vaccine Advocacy Coalition (AVAC) has released a critical assessment of progress towards this goal. Released on 18 May, the anniversary of Clinton's declaration (commemorated as World AIDS Vaccine Day), this year's report—"Six Years and Counting: Can a Shifting Landscape Accelerate an AIDS Vaccine?"—highlights the sense of optimism that has begun to permeate the field, while cautioning that "this moment of confidence must not be squandered, but used to confront the considerable challenges ahead." AVAC lays out seven principles it believes should guide vaccine development, and makes targeted recommendations for advancing the effort, emphasizing community involvement, coordination between stakeholders and government leadership. The full report can be read online at: http://www.avac.org/ readings/newestreprt.htm or ordered by calling +1 (202) 387-5517.

Online Début for AIDS Vaccine Trial Databases

Attempting to fill a gap that has plagued the AIDS vaccine field, several groups plan to release collections of information on human AIDS vaccine trials. Both IAVI and the Vaccine Research Center (Bethesda) seek to include all AIDS vaccine trials worldwide, both ongoing and completed. IAVI's information (www.iavi.org) is available as a searchable database with descriptions of the vaccine product and trial protocol and information on community contacts for enrollment. Barney Graham, Clinical Director at NIH's new Vaccine Research Center (see p. 13, this issue) and director of NIH's previous Phase I and II AIDS vaccine trials network (the AIDS Vaccine Evaluation Group), has compiled a table listing the trials along with a scientific description (www.vrc.nih.org). Later this year, amfAR (the American Foundation for AIDS Research; www.amfar.org) will release a directory of ongoing trials.