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AIDS and Vaccine Development in Asia

With the epidemic belatedly taking off in many parts of Asia, Thailand—where it began much earlier—leads the way in prevention and vaccine development

BY PATRICIA KAHN AND IAN GRUBB

The Asia-Pacific region is the world's largest and most diverse in terms of geography, populations, cultures, and political and economic systems. Stretching halfway across the globe, from Iraq to Tahiti, it is home to the world's most populous countries—China, India, Indonesia—as well as some of the smallest and most isolated, the island states of the South Pacific.

The region is also home to a belated, but now burgeoning AIDS epidemic, as several meetings and reports in late 2001 made clear. About 7.1 million Asian people are living with HIV/AIDS, over one million of them infected just within the past year (UNAIDS, December 2001; www.unaids.org/epidemic_update/report_dec01). Much of the increase was in the region's giants, India and China, where new data also document HIV's spread from severely affected high-risk groups (injecting drug users, sex workers and migrant laborers)—some with prevalence rates over 50%—into the general population (see also MAP report; http://www.unaids.org/hivaidsinfo/statistics/MAP).

Overall prevalence is still relatively low in Asia, where more than 60% of the world's population live. But speaker after speaker at the International Congress on AIDS in the Asia-Pacific (ICAAP, Melbourne, 5-9 October 2001) and India's International Conference on HIV/AIDS (16-19 December, Mumbai) projected that these early-stage epidemics will burgeon into tens of millions of new infections within the decade, leading Asia to eclipse sub-Saharan Africa as the region with the world's highest number of HIV-infected people.

Adding to the grim picture was the backdrop of the two meetings: the US bombing of Afghanistan began during ICAAP, which took place four weeks after the World Trade Center attack, while the

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PHASE I TRIAL BEGINS ON HIV-DNA/MVA PRIME-BOOST

BY EMILY BASS

In November 2001, clinical studies continued in Oxford, UK on an AIDS vaccine strategy that uses a naked HIV-DNA construct followed by a second, MVA-based (modified vaccinia Ankara) vaccine. Participants in an earlier trial of the HIV-DNA (begun in August 2000) were invited to enroll in the new study, which will test the safety of MVA as a "boost" and begin examining whether the combination elicits better immune responses than either vaccine alone. The protocol calls for two injections of 5×10^7 plaque forming units of HIV-MVA. So far, nine volunteers have received MVA boosts.

This trial is the first to test a DNA-MVA prime-boost vaccine regimen for HIV in humans. The vaccines were designed at the University of Oxford through an IAVI-sponsored partnership also involving the University of Nairobi.

Both the DNA and the MVA vaccines have been studied individually in Phase I studies in Oxford, and the DNA vaccine was also tested in Nairobi. The latter trial concluded with the last protocol visits at the end of November 2001. A protocol for a Phase I MVA trial in Nairobi has been approved by Kenyan regulatory authorities.

The new Oxford trial will start the process of determining the optimal dosing and immunization schedule for this prime-boost strategy. If results look promising, IAVI will work toward a Phase III DNA-MVA efficacy trial in Africa, which could start by the end of 2004. ◆

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Mumbai conference began within days of the Indian Parliament bombing and the resulting escalation of tensions with neighboring Pakistan. Corridor conversation focused largely on discussions of how these events have changed the global landscape and affected government priorities for attention and resources, just as many countries face ballooning numbers of sick and dying people, and of affected families and communities.

Alongside the dire predictions was a recognition that strong preventive measures implemented quickly could go a long way towards blunting the coming wave of infections, while vaccines are key in the longer term. But many countries in the region have not mounted comprehensive prevention programs, and few have prioritized AIDS vaccine development. There are exceptions: decreasing prevalence among pregnant women in Cambodia suggests that efforts to stem HIV spread are starting to pay off, while Australia and the Philippines show continued success in keeping infection rates low. China and India have both launched HIV vaccine projects, and a major initiative is underway in Australia (see page 6).

> "Thailand's success shows that we're not helpless against HIV."

But for the biggest success stories on these fronts, eyes at both meetings turned to Thailand. National prevalence rates (now just over 2%) have dropped by 80% over the past decade, and it is estimated that the country's early response—which combined intensive epidemiological surveillance, high-level political commitment, pragmatic efforts to curb the demand for commercial sex, and harm-reduction approaches such as the "100% condom program"—prevented between 1 and 2 million infections.

"Thailand's success shows that we're not helpless against HIV," says Tim Mastro, head of the US Centers for Disease Control (CDC) HIV vaccine unit in Atlanta, and formerly of the CDC's Bangkok unit. "We really can do something to stop this virus."

Thailand's Vaccine Agenda

From early on, microbicides and vaccines were seen as key, albeit future, weapons in the country's response to HIV/AIDS. By 1992, Thailand—with its extensive field experience in testing other vaccines--committed to preparing for efficacy trials, with crucial support from the World Health Organization's Global Programme on AIDS, then headed by Jonathan Mann. In this issue we highlight Thailand's current AIDS vaccine activities, drawing on discussions with the principals in Bangkok as well as presentations at ICAAP, Mumbai, the "AIDS Vaccines 2001" conference in Philadelphia (see page 13) and Thailand's International Conference on HIV Vaccines (Bangkok, 23-27 July 2001). (Additional coverage of the Mumbai meeting will be included in our next issue.)

At present these activities are centered on the ongoing Phase III trial of VaxGen's gp120-based vaccine (see page 3)—one of only two AIDS vaccine efficacy trials worldwide--and the prime-boost efficacy study planned for late 2002 (see page 4), which will be a large, community-based trial in Thailand's south (see page 4 and interview with Supachai Rerks Ngarm, page 7). Both come after nearly a decade of planning, building capacity and carrying out smaller studies: of the 13 Phase I and II HIV vaccine trials in developing countries to date, 7 were done in Thailand. Down the road, a new Australian prime-boost strategy based on Thai subtype E strains should undergo Phase I testing in 2004, while a Japanese-Thai collaboration is developing HIV vaccines based on the bacterial vector BCG.

But some Thai researchers are wary that the "success story" label can breed complacency towards today's challenges. Thailand has nearly one million people living with HIV/AIDS, and providing care—let alone making anti-retrovirals widely available—is a formidable task now facing the public health system. Another is curbing the still-rampant epidemic in IDUs, where HIV prevalence has barely changed over the past decade even as it dropped in virtually all sexual risk groups. While Thailand is almost alone within Southeast Asia in offering methadone treatment for heroin withdrawal, it has yet to move towards other harm-reduction measures, such as wide-scale needle exchange programs or long-term methadone maintenance, that could have a real impact. In a region which is flooded with plentiful, cheap heroin, reducing HIV spread in IDUs is crucial not just for Thailand's epidemic but for that in neighboring China, Vietnam, India and Myanmar.

There is also concern over a possible resurgence in new infections, given the low rates of condom use by steady couples and the fact that young men increasingly seek partners among peers rather than commercial sex workers; vaccine preparedness studies in southern Thailand recently found that young married women now represent one of the highest-risk groups (see page 4). On the political front, Thailand is still operating without an AIDS vaccine subcommittee, which was dissolved last summer amid renewed disputes over Phase III trials of the Remune therapeutic vaccine (see *IAVI Report* Dec. 2000-Jan. 2001, p. 20), temporarily shutting down a key component of the approvals pathway for clinical studies just as the next Phase III trial is being prepared.

In the longer term, Thailand's role in HIV vaccine testing is also changing. With heterosexual transmission rates dropping to a level that makes future efficacy studies difficult in this population, the country may focus on higher-risk groups and early-stage trials. In a "Viewpoint" article (see page 9), Bangkok-based vaccine developer Jean-Louis Excler advocates building Phase III testing capacity in neighboring countries that are now experiencing more severe heterosexual epidemics. While acknowledging the difficulties of working in places with far less infrastructure and political commitment than Thailand's, he argues that closer collaboration between international players and among local stakeholders are essential missing ingredients.

Within Thailand, another worry is the sparsity of

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VaxGen's Phase III Trial: Working with a Drug User Cohort

BY PATRICIA KAHN

Thailand's launch of the VaxGen Phase III trial in March 1999 represented another "first" for a nation that has been one of the world's most pro-active in efforts to reduce the spread of HIV. But beyond its being the first AIDS vaccine efficacy study in a developing country, the ongoing trial is breaking ground on another front of the prevention battle: finding ways to successfully reach, engage and retain large numbers of injecting drug users (IDUs)—a key population fueling the Asian epidemic, but one often viewed by vaccine developers as too difficult to work with for efficacy trials lasting several years.

"The trial is showing that you *can* follow injectors," says epidemiologist Chris Beyrer of the Johns Hopkins School of Public Health. "The cohort has much better retention than many other high-risk cohorts, such as commercial sex workers. This is really important." Beyrer, an expert on the AIDS epidemic in Southeast Asia, has long argued that the high prevalence and rampant spread of HIV in Asia's IDU populations means that "if a vaccine doesn't work in IDUs, we won't stop the epidemic."

At the 2001 meetings cited on page 2, plus an *IAVI Report* visit to the Bangkok Vaccine Evaluation Group (BVEG, the consortium of trial collaborators) and to the study site at Taksin Hospital, trial investigators discussed the study's progress, its 2,545-person cohort and some of the factors that help make it work.

Building the Foundation

The cohort is rooted in Bangkok's methadone treatment centers for heroin users—a rarity in Asia, where drug addiction is nearly always a matter for imprisonment and addicts are left to "cold turkey" withdrawal. (Across Asia, methadone is only available in Thailand and Hong Kong.) Bangkok is an exception: in 1980 the Bangkok Metropolitan Authority (BMA) opened a network of outpatient clinics where addicts can undergo a 45-day detoxification program with decreasing doses of methadone to help them get off heroin. While this approach alone has not solved the problem—there is a high rate of relapse, and long-term methadone maintenance is not available—it is a crucial step towards tackling addiction as a public health problem rather than a criminal one. Every year about 8,000 addicts (70% of them injectors) seek treatment through this system.

The present trial grew out of work begun in the early 1990s, when alarm over the country's exploding HIV epidemic, and support of the World Health Organization's Global Programme on AIDS, led Thailand's public health and scientific communities to begin building capacity for HIV vaccine trials—and to view the BMA clinics as a possible setting. The AIDSVAX® vaccine now in Phase III trials existed in a simpler form made from HIV subtype B, then the predominant subtype in both Thailand and the US, and was being moved by Genentech (VaxGen's parent company) towards US government-sponsored efficacy trials.

But in 1994, when the US decided against funding a Phase III trial—based on the vaccine's failure to neutralize primary (rather than laboratory-grown) strains of HIV—Thailand's scientists remained interested nevertheless, on the grounds that success or failure of past vaccines (including some tested in Thailand) was often not predictable from laboratory tests. The next year, the BMA, along with Tim Mastro at the US Centers for Disease Control's (CDC) Bangkok unit, Mahidol University, WHO and UNAIDS, established a 1,200-person HIV-negative vaccine preparedness cohort in the 16 methadone clinics to determine HIV incidence, identify key risk factors for infection and assess volunteers' willingness to participate in vaccine trials. HIV prevalence at screening for enrollment was 30%, and the incidence of new infections in the cohort (followed through 1998) was 5.8 per 100 person-years, despite intensive prevention counseling. Surprisingly, the study also found that 79% of all new infections were with HIV subtype E, which by then predominated in heterosexual transmission in Thailand but reflected a major shift in the Bangkok IDU population away from subtype B. This finding led to a re-design of AIDSVAX® to incorporate subtype E gp120 alongside gp120 from the original lab-grown subtype B.

The preparedness study also found that infection risk in this group was strongly associated with injection behavior rather than sexual risk, even in the cohort's few women (although womens' overall risk was higher). Needle exchange remains unacceptable in Thailand and is not possible even within the trial setting. Although volunteers commonly obtained sterile needles and syringes from pharmacies, where they are widely available for low prices, sharing remained a key risk factor, probably stemming partly from volunteers' fear of arrest if caught with injecting materials. Furthermore, over 43% of the volunteers reported being incarcerated at some point during the study, and injecting while in prison was a key source of infection—especially for people going through withdrawal, whose desperation can lead them to ignore clear risks, according to BVEG's Suphak Vanichseni.

> "The trial is showing that you can follow injectors."

The Trial Cohort

Moving from the preparedness work to the Phase III cohort went fairly smoothly, says Vanichseni, although recruitment took a few months longer than anticipated—due partly to a drop in the number of injectors in Bangkok, a trend accompanying the steep, nationwide rise in methamphetamine use. To compensate, the trial team added two mobile units and did additional recruiting farther afield of Bangkok proper.

As with the earlier cohort, the study population

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◀ **VAX-GEN TRIAL** *continued from 3*

consists largely of people with more stable lives than common stereotypes of IDUs suggest. About 70% are employed (30% in stable jobs), many as motorcycle taxi drivers, others as day workers in manual occupations, and over 60% have steady partners. The cohort is overwhelmingly male (93.5%), and most of the enrolled women are partners of other volunteers. While "a certain group of the IDUs is marginalized," says Frits van Griensven of the Bangkok CDC, which collaborates on the trial, "most lead rather normal lives." According to Pakorn Sukklam, a counselor at the Taksin Hospital site, very few resort to criminality to buy heroin, which is available relatively cheaply, and in much purer form, compared with Western countries. This stability is reflected in the cohort's very high retention rate: 97.4% at one year, says Vanichseni.

At the IPAAC meeting, Vanichseni presented a summary of risk behaviors in the cohort. At the trial's start (baseline), methadone treatment alone had reduced injection frequency from 3-4 times to once daily on average, but 94% of the volunteers reported injecting within the past 6 months; one year into the trial, the figure was 72%, with 16% reporting needle-sharing (33% at baseline). Incarceration remains frequent, but—a key factor in the trial's high retention rate—a long-negotiated arrangement with police allows trial staff to conduct follow-up visits with imprisoned volunteers.

Kachit Choopanya, the trial's principal investigator, also attributes the high retention rate to the bond between participants and trial counselors. "It's a holdover from methadone treatment, when the volunteers saw their health care worker every day," he says. "That creates a very trusting relationship, and is one of the main reasons we can retain people." Counseling sessions take a harm-reduction

THAILAND PREPARES FOR A NEW PHASE III TRIAL

BY PATRICIA KAHN

US and Thai researchers plan an ambitious trial of a prime-boost vaccine strategy using canarypox and gp120, to begin within the year.

As the three-year VaxGen trial in Bangkok approaches its midpoint (see article, page 3), Thailand is already deep in the midst of preparations for a second Phase III AIDS vaccine study. Slated to begin in the latter half of 2002, the trial will test whether a "prime-boost" strategy combining two vaccines—the first containing HIV genes in a canarypox virus vector (Aventis Pasteur's vCP1521 construct), followed by VaxGen's envelope (gp120) protein subunit—can protect against heterosexual transmission. If it proceeds as planned, the trial will be the only the third AIDS vaccine efficacy study worldwide, and the first to test a prime-boost strategy and to use a community-based population (rather than selected high-risk groups).

In the US, the HIV Vaccine Trials Network (HVTN) is planning a similar Phase III trial using vCP1452, a later version of the canarypox vaccine, which would start in 2003 at sites in the US and Latin America (see article, page 14). The two trials differ in design, and their teams are conferring on how to ensure that data can be pooled or compared.

In presentations at the meetings reported here, researchers involved with the Thai trial—a collaboration of the US and Thai Army vaccine programs, Mahidol University and Thailand's Ministry of Public Health—described plans for what will be an enormous logistical undertaking, involving over six times more volunteers than the ongoing VaxGen trial (16,000 versus 2,500). They also presented results from community-based cohort studies that shaped the trial design, as well as preliminary data from a Phase II trial that will guide the final "go-no go" decision on Phase III. And they made their case for moving ahead, provided that the final Phase II data meet scientific milestones set earlier—although there are conflicting opinions in the field as to whether the immunogenicity criteria (essentially the same as those for the US trial) are stringent enough, and the canarypox vaccines promising enough, to justify moving forward. The *IAVIReport* will continue to follow the pivotal decisions on these two trials as they unfold over the coming months.

The Road to Phase III

At the Bangkok meeting, Michel Klein of Aventis Pasteur summarized the long pathway that has brought the HIV-canarypox vaccines to the brink of efficacy trials. Developed from a vector that has been used successfully to make several veterinary vaccines, clinical testing began in the late 1980s, with more HIV components added to the vaccine over time. Cumulatively, HIV-canarypox constructs have now been tested in over 40 Phase I and II studies involving about 1900 volunteers, and show an excellent safety record. Over 700 of those volunteers have been in Thailand, where the US-Thai collaboration began testing these vaccines (with different protein boosts and immunization regimes) in 1995.

In terms of immune responses, clinical studies have looked mostly for CD8+ T-lymphocytes (CTLs) that specifically kill HIV-infected cells. Overall, CTLs are found in blood samples from 20-40% of canarypox-vaccinated people, and in some cases the CTLs are still detected 2-3 years after the last immunization, according to Klein. About two-thirds of vaccinees also show LPR (lymphoproliferative responses, which primarily detect T-helper cells) and neutralizing antibody responses to laboratory-grown HIV, but much less neutralization of primary HIV strains.

The final decision on launch-

approach to lowering HIV risk, starting with discussions of stopping injection altogether, then moving to reinforcing the importance of sterile equipment, and ways of sterilizing used equipment with bleach, and to counseling on safe sex.

Other Trial News

As 2001 drew to a close, there were two new developments in the trial. On 1 October, the BMA officially changed its treatment recommendations for HIV-infected people from two-drug therapy to HAART, and the trial—which linked its treatment policy to the BMA's—followed suit. According to Jordan Tappero, who heads the CDC's Bangkok unit, volunteers who became infected during the trial and have already started on two anti-retrovirals (for CD4 counts below 500) were switched to a three-drug regimen; since 1 October, HIV-infected volunteers naive to ARVs are being offered HAART when their CD4 count falls below 200, or for symptomatic HIV infection. Although Thailand's national guidelines on AIDS treatment call for HAART, in practice the public health system cannot pay for it, and only a few thousand Thais (mostly self-paying) receive triple-drug therapy.

Second, the CDC has launched a sub-study of HIV transmission in participants who become infected (drawn from both the placebo and vaccine arms, which are still blinded). Volunteers and their partners are invited to enroll for intensive counseling on avoiding transmission, analysis of HIV subtype and monitoring of viral parameters (such as viral load in blood and semen) to look for possible vaccine effects on transmission rate.

An interim data analysis will be done in late 2002. The trial is scheduled to run mid-2003. ◆

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ing Phase III testing will be based on whether results from an ongoing Phase II study (RV135) in Bangkok meet immunogenicity milestones. These are: a CTL response to selected antigens of HIV subtype E, the predominant clade in Thailand, in at least 30% of vaccinated volunteers at one or more time points (called a "cumulative" CTL response); LPR in 60% of vaccinees; and neutralizing antibodies to a standardized laboratory-grown HIV strain in 70%.

In a poster presentation at the Philadelphia conference, Mark de Souza of the US Army group in Bangkok (the Armed Forces Research Institute of Medical Sciences, or AFRIMS) presented preliminary results from RV135, which uses the exact vaccine combination and immunization regimen being proposed for the Thai efficacy study. The protocol calls for vCP1521 (which contains gp120 from an R5 subtype E HIV strain, plus gp41 and *gag/pro* from subtype B) to be given at weeks 0, 4, 12, and 24, along with a boost of VaxGen's bivalent B/E gp120 (at weeks 12 and 24, in two dosage groups) in 90 volunteers; another 30 received placebos. With the data still blinded and some late study visits and assays incomplete, De Souza reported cumulative HIV-specific (Env or Gag/Pro) CTL responses in 20 of 117 volunteers.

These numbers suggest that, even with the placebo group removed, it will be close in terms of meeting the 30% CTL milestone. And it is here that the controversy over moving to Phase III lies: the relatively low proportion of CTL responders in past trials, and the fact that responses often seem weak (although the CTL assay is poorly quantitative) has led some researchers to doubt the rationale for moving forward.

In their meeting presentations, and in conversations with the *IAVI Report*, Army researchers argued otherwise. John McNeil (Walter Reed Army Institute of Research) reminded the Philadelphia audience that the canarypox vaccines are the only ones sufficiently well-studied to move into Phase III within the next two years or so. Art Brown, who leads the AFRIMS group in Bangkok, sees potential limits on the CTL assay, which looks at cells from the peripheral blood rather than the lymph nodes. "It may not be the right way to sample," he says—although unfortunately it's the only feasible way for now. At the same time, Marta Marthas (University of California at Davis) has new data showing that—despite the lackluster CTL data in humans— a canarypox-based SIV vaccine protected 6/8 neonatal monkeys against multiple low-dose oral challenge with pathogenic SIV (see article, page 11).

And from the Thai perspective, Supachai Rerks Ngarm of the Ministry of Health, a principal investigator of the trial, points out that Thailand sees even a fairly low-efficacy vaccine as a useful weapon in battling against AIDS (see interview, page 7).

Since the Philadelphia meeting, the Phase II data have been completed and are under discussion among the collaborators, according to McNeil, although they have not yet been presented publicly. But as the *IAVI Report* went to press, he gave no hint of any change in plans, saying that "the Army remains committed to moving forward with the trial, together with our Thai partners."

HIV INCIDENCE IN THE CHON BURI PREPAREDNESS COHORT

Age group	HIV incidence (# new infections per 100 person-years)
20-24	0.37
25-29	0.98
>30	0.22
overall	0.54
combined 20-30	0.68 (95% confidence interval: 0.34-1.02)

Data from Michael Benenson (AFRIMS, Bangkok)

Preparing Cohorts

At the Bangkok conference, Mike Benenson (AFRIMS) presented results from cohort studies aimed at finding suitable and willing populations for the trial, and at developing the necessary infrastructure.

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New in the Pipeline: Australia's Prime-Boost Vaccines

BY IAN GRUBB

New fowlpox-based vaccines, together with a DNA vaccine prime, are slated for clinical trials in Sydney and Bangkok

With HIV vaccines based on canarypox poised to enter Phase III studies (see articles on pp. 4 and 14), a new prime-boost strategy using a related viral vector is just entering the clinical development pipeline. At the Bangkok and Melbourne meetings, researchers from an Australia-based consortium reported on their program to combine a DNA vaccine prime with a new HIV vaccine made from fowlpox, and possibly also with a cytokine (an immune-enhancing "messenger" molecule). The strategy is designed to work by inducing T-cell responses, with little or no contribution from antibodies.

With design and production work in full swing, the first Phase I study in HIV-negative volunteers is expected to begin in Sydney in August, 2002 using a "proof of concept" clade B construct. A second trial with a subtype E-based vaccine is planned for the following year in Thailand. A therapeutic trial of an HIV-fowlpox construct carrying the cytokine interferon-gamma was launched last year in Sydney and has so far enrolled 27 of a planned 36 newly HIV-infected people.

Led by David Cooper, director of the National Centre in HIV Epidemiology and Clinical Research (NCHECR) at Sydney's University of New South Wales (UNSW), the project is organized as a consortium of public and private sector collaborators, including several academic research centers, social researchers, a biotechnology company and community groups. Funding comes from a US$ 16.7 million grant from the National Institute of Allergy and Infectious Diseases (NIAID) under its HIV Vaccine Design and Development Team (HVDDT) program, which covers development and testing of the concept over five years (2000-2005). The Australian researchers are the only group outside the US to receive HVDDT funding so far, and the NIAID grant is among the largest ever for Australian biomedical research. Under the contract, no decision to commercialize the product, should it prove successful, can be made without consensus of all consortium members.

The Vaccine Designs

The DNA vaccine prime, developed by Ian Ramshaw's group at the Australian National University in Canberra (based on technology developed by Heather Davies and colleagues, and licensed to Coley Pharmaceutical Group) contains *gag-pol* sequences as well as the *env*, *tat* and *rev* genes. It also includes bacterial sequences called CpG motifs that are known to enhance immune responses.

The "boost" component is based on a recombinant fowlpox vector (rFPV) that has been used for several poultry vaccines. The fowlpox platform was developed by David Boyle and colleagues at Australia's Commonwealth Scientific & Industrial Research Organization (CSIRO), based outside Melbourne. The version used in the Sydney trial will contain *gag-pol* and *env*, and possibly a cytokine (interferon-gamma or IL-12). It may be further refined for the Thai trial.

In his ICAAP presentation, David Boyle (CSIRO Animal Health) described fowlpox as one of the largest known viruses, capable of accepting very large genetic inserts. It can be grown to higher titers than its relative, canarypox, but is also difficult to produce on a large scale. Both Boyle and Cooper expressed the view that there will eventually need to be head-to-head comparisons of these and other viral vectors.

Animal Model Studies

For the sake of speed, the Australian group has tested the HIV vaccines directly in monkeys rather than constructing SIV equivalents, based on earlier work probing the utility of this approach for answering certain questions. Using this system, Stephen Kent (University of Melbourne) found that the prime and boost vaccines induce significant CTL and T-helper cell responses when given together, but not singly. He also showed that they protect macaques against acute infection after challenge with non-pathogenic HIV. Challenge studies with a pathogenic SHIV are now in planning.

Kent also described ongoing work in macaques to evaluate other potential vaccine components, including CpG motifs, additional HIV antigens, and cytokines (interferon-gamma or IL-12). The latter studies are based on a co-expression technology (Co-X-Gene™ with FPV) being developed under license from the CSIRO and the Australian National University by the Melbourne-based biotech firm Virax Immunotherapeutics Inc. The outcome of these macaque studies, and of the ongoing therapeutic trial, should clarify whether to include a cytokine in the final vaccine design.

Phase I/II Trials

At the ICAAP meeting, Sean Emery (NCHECR), coordinator of the project's trials and laboratory monitoring, reported that the protocol for the Sydney study is almost ready for submission to Australia's Therapeutic Goods Administration (TGA), NIH and the Institutional Review Board at Sydney's St Vincent's Hospital Medical Centre, where the trial will take place.

The study will begin with a "vanguard" cohort of 8 low-risk volunteers, a requirement of the TGA, and then scale up to 42 participants divided into three arms: placebo (n=6); DNA prime + FPV boost (n=18); and DNA prime + rFPV/cytokine (n=18). DNA will be given at weeks 0 and 4, followed by FPV at week 8, and participants will be monitored for 52 weeks. Primary endpoints will be safety and im-

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Thailand, AIDS and Vaccines

Dr. Supachai Rerks Ngarm is currently Senior Expert in Preventive Medicine in Thailand's Department of Communicable Diseases, Ministry of Public Health, and a principal investigator of the prime-boost Phase III vaccine trial due to start in 2002 (see article, page 4). A pediatrician and epidemiologist trained at universities in Thailand, Singapore, Israel, Canada and Japan, he was chief of outbreak investigation in the epidemiology section of the Ministry (1985-90) and then became the first director of its new AIDS division during the period when Thailand launched its aggressive HIV prevention program. In 1997, he became coordinator of Thailand's polio eradication program, and has also led efforts to improve immunization services.

AN INTERVIEW WITH

Supachai Rerks Ngarm

Before we talk about the upcoming trial, can you give us some background on how Thailand became so pro-active in AIDS prevention, including vaccines, early in its own epidemic—while so many other countries were doing little to stem HIV spread?

Looking back it seems like it was very easy. But at the time, there were many problems convincing people at the highest levels to take action. The pioneer was Dr. Prayura Kunasol, who was in charge of epidemiology at the Ministry of Public Health. The first case of AIDS was recognized in Thailand in 1984, and from that point on, he began trying to persuade key people in government that this new disease posed a great danger to our country. He was the one of the group who set up a country-wide surveillance system, which became the root of our prevention program.

And the early commitment to AIDS vaccines?

This was a natural step for us, since our country has a great deal of field experience testing other vaccines, such as hepatitis B and Japanese encephalitis vaccine. In 1990, the World Health Organization, through Jonathan Mann, was looking for countries that could carry out AIDS vaccine trials. Our Ministry of Health was very responsive to this. That started the process, first with the formation of a working group, chaired by Professor Prasert Thongcharoen to recommend whether Thailand should do this, and then in drafting national guidelines on how to review and conduct trials.

Can you describe the approvals process for the upcoming Phase III trial?

We have a 2-step process. First is an informal consideration by the scientific subcommittee on AIDS vaccines. They will review our protocol and then send feedback to us for modifications. If we agree on this, we will resubmit to the subcommittee so they can officially consider the protocol. They can then say that it's approved, or that it's not approved, or needs further changes. Then we modify the protocol according to their recommendations. Probably in parallel to this scientific review, we can submit our proposal to the ethics committee.

Has this process begun yet?

Our protocol was reviewed at the Walter Reed [Army Institute of Research] and we have made some modifications. We are now preparing for review by the Thai vaccine subcommittee. Sad to say, at the moment we don't have the new subcommittee, which is still in the process of being re-established.

Will this subcommittee use the same scientific milestones as the US partners for approving the trial?

We have about the same criteria for our decision-making. If it seems that the trial is not going to have any success, the subcommittee will not agree to move ahead.

But for us the exact percentage of vaccinees who respond is perhaps not so strict. Because of the epidemic here in Thailand, even a vaccine with 30% efficacy is still useful for us. But it would be just one element of our prevention efforts. We don't expect that the first vaccines will be 100% effective, that they will be a magic bullet which eliminates the need for other interventions. We see vaccines as a tool which complements other interventions.

Do you worry that a vaccine that is, say, 30% effective might create a false sense of security so that vaccinated people actually increase their risk behavior?

It depends on how you tell people. We will always tell them that they must stay aware and avoid any risk—always.

What are the plans for involving local communities in the trial?

We will try by all means, by every approach, to have the community with us. A community advisory board [CAB] will be one thing. We also plan to have sessions where we talk with community leaders, formally and informally, to explain the importance of this trial and what they can do for the program.

Among Thais, especially the senior people—in terms of both age and social standing—respect is very important. If we go to the leaders and ask for their ideas, their interpretation would be that we respect them, and they would be very proud and pleased to help us. This is the way of Thai culture, that youngsters should pay respect to the senior people. We will try to do that.

How will the CABs be set up?

We will probably recommend that every district has

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AUSTRALIAN PRIME-BOOST VACCINES *continued from 7*

nunogenicity, as measured by ELISPOT and lymphoproliferation assays, with other immune assays likely to be added. GMP manufacture of both the DNA component (under subcontract to the German firm Qiagen Inc.) and the rFPV vaccine (by IDT Limited in Melbourne) is complete.

Design of the Thai study will be informed by the results from Sydney. The trial will be carried out under the banner of HIVNAT, a partnership of HIV clinical researchers from the Netherlands, Australia and Thailand, together with the Thai Red Cross, with whom Cooper has an ongoing clinical study on anti-retroviral treatment in 1,000 volunteers.

Beyond immunology

The vaccine development consortium also includes the National Centre in HIV Social Research (NCHSR) at Sydney's UNSW and the Australian Federation of AIDS Organisations (AFAO), who will take the lead on socio-behavioral and ethical issues. Over the next few years, the NCHECR group plans to enroll up to 500 HIV-negative men in an open cohort vaccine preparedness study called "Health in Men (HIM)." The study will examine the relationships between trials and risk behaviors, help researchers understand what motivates people to join trials and guide AFAO—the national umbrella group for Australian AIDS NGOs—in developing future HIV prevention programs.

Beyond ensuring that the trials incorporate strong risk behavior prevention strategies, AFAO is collaborating with the project's biomedical researchers on community needs and ethical concerns. Outgoing AFAO Executive Director and ICAAP Co-Chair Robin Gorna also reported on plans to partner with a Bangkok NGO to support community participation in the Thailand trial. ◆

◀**RERKS NGARM INTERVIEW** *continued from 7*

its own CAB, and also that the local NGO sits on this board. It will include representatives of the trial participants, as well as other interested parties such as community leaders and people living with HIV.

Do you expect the press to follow the trial closely?
Our intention is to be very open to the press. We are planning some publicity activities, some community involvement activities. We have already held one media education session, and plan to do this kind of informal meeting with national and local media, probably about every two months. Besides these planned sessions, we will encourage journalists to come to us any time if they have questions.

What treatment will be available to volunteers who become infected during the trial?
We have recently made triple drug therapy the national standard, although because of the cost it isn't yet possible to make it widely available. But for the trial, the Walter Reed has committed to funding triple therapy for intercurrent infections. And the Thai government can provide the infrastructure for making treatment available over the long term.

Since Thailand has had such success in reducing HIV spread via heterosexual transmission, future vaccine trials in community cohorts would require much larger numbers of volunteers. Do you think there will be further Phase III trials in Thailand?
This is the most difficult part of our planning. But the decrease in AIDS incidence is a national average. We still can find regions that tend to be high, or at the beginning phase of HIV spread.

Incidence is also very high among injecting drug users [IDUs] in Thailand. So I don't think that this will be our last Phase III trial. But I have to admit that the next trial will probably be more difficult than this one.

Even this trial, I don't think it will be easy at all. Scaling up to tens of thousands is not easy. Since the trial will have about 16,000 participants, we may need to screen 25-30,000 potential volunteers.

You mentioned the very high infection rate in injecting drug users, which hasn't changed much even as heterosexual transmission rates have come way down in Thailand. How are you tackling this now?
This part of the epidemic, I have to admit, is the most difficult one for us. Needle exchange programs are not acceptable to our society, but very quietly we are working with some local NGOs to test this approach and see if it works.

Previously we thought that the IDU group was just a small fraction of our society, and that at least we had a methadone program in every big city and in big provinces. We used this service as an entry point for people to access HIV prevention information.

But even though we have behavioral studies that help us understand *why* people share needles, we still couldn't change their behavior. You can buy needles without a prescription here in Thailand, but people don't want to do that because it can probably be used as evidence against them [if they are arrested on drug charges]. To solve this problem we need to work together, not only within the health sector, but with the police department. We have a very long history with them, not only on IDUs, but also sex workers.

Getting back to vaccines, the cohort studies done in southern Thailand as preparation for the Phase III trial found a very high level of willingness to participate among the local people. Why do you think this is so?
I think that our people, especially in the rural areas, realize what a serious problem we have with AIDS, and they are expecting that there should be something to protect them. I think they also want to help society. Vaccines give people a feeling of hope.

As Buddhist people, we try to do good things while we are alive, since this is what the Lord Buddha taught us. I believe that people think this is one of the good things for their life: to help people and to make our generation safe. ◆

HIV VACCINE DEVELOPMENT NEEDS MORE FOCUS AND CLOSER COLLABORATIONS

VIEWPOINT

BY JEAN-LOUIS EXCLER

Jean-Louis Excler is a pediatrician and epidemiologist who became involved in immunization programs while working in Africa, where his six years included a stint as chief of UNICEF's Expanded Program of Immunizations and Primary Health Care in the Central African Republic. He became involved with HIV vaccines upon his return to France in 1991 as chief of HIV vaccine clinical development at Pasteur Mérieux Connaught (now Aventis Pasteur). In 1998, he moved to the Henry M. Jackson Foundation in Rockville, Maryland, where he worked on the US Army's HIV vaccine program, then moving to Bangkok to help prepare for the Army's Phase III efficacy trial. He now consults for UNICEF on issues surrounding HIV and safe motherhood in the East Asia/Pacific region.

Over the past few years, effort and commitment to develop an AIDS vaccine have gained a great deal of momentum in many countries and international agencies. Much of the activity is happening in American, European, Australian and Japanese institutions, but a growing number of less developed countries—including Thailand, South Africa, Uganda, Kenya, China, Brazil, India, Trinidad & Tobago, Haiti and Cuba—are also participating, despite their poverty and often difficult political and logistical conditions.

Yet twenty years into the epidemic, we must ask why we aren't farther along in this endeavor. Are the different worldwide efforts always well-focused on the challenge, which is to make available an effective, affordable HIV/AIDS vaccine? Are we putting enough effort into reasonable vaccine approaches that already exist and could be tested in the field, and into building trial site infrastructures in highly affected countries, or are our efforts too scattered?

My answers to these questions are based on the premise that vaccine research is distinct from vaccine development, and that most activity over the past two decades has focused on vaccine research. While some of this research is critical to feeding the development pipeline upstream, at other times it seems detached from the emergency of the epidemic and the public health task at hand. My sense, after ten years working on this problem in academic, industry and government settings, is that the task requires much more attention to product development and to collaborating more effectively on driving a limited number of vaccine approaches more forcefully through the pipeline.

What are some specific areas where greater focus and collaboration could accelerate vaccine development? One is manufacturing. This is a serious bottleneck even at early stages of vaccine clinical testing (when only small pilot lots of vaccines are required), since most candidate vaccine manufacture is subcontracted to biotechnology companies with very limited production capacity. The longer-term picture may be even worse for all but the few vaccines being developed by big pharmaceutical companies, since small production units cannot support the large-scale manufacturing needed for Phase III trials.

There are certainly no easy fixes to this problem. But there is little effective concentration of production efforts, know-how or funding to develop sorely needed capacity in GMP (Good Manufacturing Practices) and QC (Quality Control). For example, there are institutions in at least six countries working on prime-boost strategies that combine HIV-DNA vaccines with MVA (or similar attenuated vaccinia vectors). These projects could benefit from a concerted focus on a limited number of manufacturing and QC units, concentrating and strengthening their capacities to meet the production needs of different products. I am afraid this is not at all the case.

The strength of a water current must reach a certain threshold to move a mill wheel. The same applies to vaccine production and development. Massive funding support to a few GMP manufacturing plants that can produce pilot lots would consequently benefit the overall vaccine effort by increasing the availability of products for testing. Another mid- and long-term approach to this problem is to involve vaccine manufacturers from developing countries. For example, India, Brazil, China, Cuba and South Africa already have capacity, while others could be upgraded to GMP and QC international standards.

Another area in need of more focused effort is preparation of vaccine trial sites. The AIDS epidemic is a moving target and therefore difficult to hit. Still, HIV vaccines need to be developed for and tested in countries where the epidemic is raging and where efficacy trials are feasible. We are facing the classical dilemma of developing cohorts without a vaccine and developing vaccines without populations for testing them.

One exception is Thailand, a country that has attracted and supported HIV vaccine developers for over a decade. This stems from the country's outstanding intellectual and technical capacities for clinical research, its political stability and strong economy, and of course the explosion of the epidemic there in the early 1990s. Continuing its pioneering role in HIV vaccine development, Thailand is now hosting the first efficacy trial in a population of injecting drug users (IDUs), in this case, with a non-clade B vaccine. A second Phase III trial—a prime-boost study of

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◀ **VIEWPOINT** *continued from 9*

canarypox plus gp120 in community-based cohorts—is likely to start in 2002 (see article, page 4), while a few other vaccine candidates are on the pathway to Phase I/II trials in Thailand.

However, the rate of new infections in Thailand has now dropped below 1% in the general population (i.e., outside high-risk groups such as IDUs and commercial sex workers). At this low rate, trials must become much larger and therefore more expensive, and it could become very difficult to conduct any other community-based efficacy tests—yet these are essential for testing vaccine efficacy against heterosexual transmission and for ensuring that large numbers of women are included in cohorts.

Soon Vietnam may face the same situation. Yet, with the exception of India and to a lesser extent China, which both recently became active in vaccine development, other eastern Asian countries have few or no vaccine efforts underway. Why not?

Several explanations can be given. One is that some of these countries were slow to acknowledge the extent of their AIDS problem. Another is that research sponsors and foreign investigators often have an insufficient, superficial knowledge of these countries, leading to concerns—legitimate or not—about whether obstacles such as local political turbulence, difficulties in build-ing technical and/or national consensus, and slower approval processes, will prove insurmountable. In addition, local power agendas may take root, especially in the absence of effective collaboration between foreign or domestic institutions and/or individuals within the country.

But such explanations for not investing in these countries are not justifications. HIV vaccine development should be a high priority in Southeast Asia, alongside HIV/AIDS prevention and care. Research and funding institutions must have the courage to commit to regions with growing epidemics, whatever the local difficulties are. None of these difficulties are insurmountable and we must accept some risk that vaccine trials may not always go smoothly.

Ten years ago, WHO (then the Global Programme on AIDS) assessed a group of developing countries regarding their willingness and capacity to participate in vaccine testing, an exercise which led to a focus on Uganda, Rwanda, Brazil and Thailand. A similar in-depth, objective assessment of countries heavily affected by HIV today should be urgently renewed by WHO, since many more countries now wish to participate and are willing to undertake the steps needed to reach international standards of clinical development.

Political will on the part of foreign sponsors, institutions and investigators and an open-minded approach towards the difficulties of local conditions are essential ingredients of working successfully in developing regions. So is recognition that vaccine trials will require a long-term commitment from foreign scientists, rather than the much more common short-term, limited collaborations involving little cost or commitment (along the lines of "Let's set up a small lab and see how things turn out").

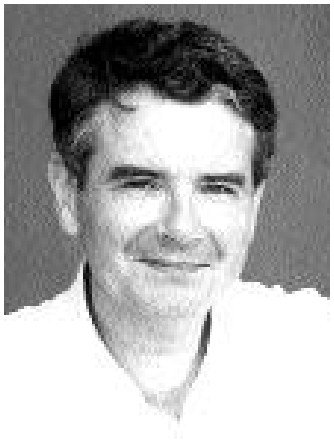
I favor a regionally-focused, integrated approach to HIV vaccine development. Countries in a given geographical area (for example, South East Asia or East Africa) should establish a task force that includes all national and international partners. This trans-agency task force should formulate a clear, specific vaccine development plan appropriate to the region, including a list of ways to establish effective interactions among the different players and to avoid situations in which different groups work in parallel without effective communication. It should also define the HIV subtype(s) to be used, vaccine concept, design and manufacturing and the appropriate and available populations for testing, along with any epidemiological studies needed to assess the feasibility of efficacy trials. The task force would prioritize the vaccine concepts to be moved forward and recommend the most appropriate countries for testing these vaccines. (One country may be more appropriate for Phase I trials, and another to test vaccine efficacy in specific types of populations.)

But effective coordination can only happen under strong leadership—the definitive gap in HIV vaccine development. How many battles against disease would have been lost without the leadership of Louis Pasteur, the World Health Organization, Médecins Sans Frontières, and many others?

Where should this leadership come from? I have no magical formula to offer, but I would say to developing country leaders: "Don't wait for a solution from outside—be bold!" The United Nations and NGOs can also help embolden highly affected countries to be effective, proactive partners in the process, and perhaps thereby to help mold new leadership.

Regions coming together in this way would have several advantages. It would allow for much bigger investments in infrastructure, technical and managerial capacity-building and cohort development. It would also help ensure that in-country people are fully involved with international partners in setting the overall vaccine agenda, not only in the late stage of designing and implementing specific trials, as is too often the case.

While these collaborations are not without their difficulties, and can be time-consuming to establish and maintain, proceeding without them could ultimately become an even bigger obstacle to the common goal of getting an effective vaccine as quickly as possible. ◆



Jean-Louis Excler

Helping Pediatric HIV Vaccines Grow Up

HIV researchers at the Pediatric Vaccine Immunology Workshop look for lessons from other childhood vaccines

BY EMILY BASS

Pediatrics and vaccinology have long gone hand-in-hand. Children, including young babies, were key participants in trials of polio, BCG and measles vaccines, all of which are now given to infants. But HIV has turned this paradigm on its head. Regulatory, ethical and scientific uncertainties have kept studies of HIV vaccines in babies largely off the agenda: So far there have been only two such trials, both in North America, while efforts to launch a third one in Uganda have been years in the making (see *IAVI Report*, July-Sep. 2001, p.3).

Yet every year, 500,000 babies—most in sub-Saharan Africa—become infected with HIV, and the explosive infection rates among young women in much of the developing world mean that these numbers will continue to grow. While wider use of antiretroviral drugs such as nevirapine can help reduce transmission at birth, these gains will be largely offset by infections occurring afterwards via breastfeeding, which remains common among HIV-positive mothers in the developing world for a variety of health and cultural reasons.

On 11-13 October 2001, 21 scientists met in Dedham, Massachusetts to assess the state of the pediatric AIDS vaccine field and look for ways to accelerate progress. Hosted by the Elizabeth Glaser Pediatric AIDS Foundation, the interdisciplinary gathering of pediatricians, vaccinologists, virologists and primate researchers found a shared goal: the need to move pediatric vaccines forward with speed. They also found—perhaps surprisingly—some reasons for optimism amid the grim statistics: Even in the first months of life, the neonatal immune system appears to be capable of robust cellular immune responses to at least some viral pathogens and vaccines.

The meeting also brought striking news from the monkey model system. New data from Marta Marthas' lab at the University of California (Davis) show that a canarypox-based SIV vaccine appears to protect infant monkeys against low-dose oral challenges of pathogenic virus—the first real evidence that a vaccine might protect newborns against repeated exposure to HIV in breast milk.

Members of the group also stressed that some vaccines may be more potent in children than in adults. The varicella vaccine, for example, induces only weak immune responses in adults, who require two doses for protection, while infants are protected after only single one. "If we had done those trials only in adults, we would have said it was not a good vaccine," said participant Ann Arvin, a pediatrician and vaccine researcher at Stanford University.

These leads solidified the consensus that HIV vaccine trials in infants should not always wait until extensive testing in adults is complete. With the tremendous need, and a growing number of vaccine candidates poised to enter the clinical development pipeline, "we need to make these trials as concurrent as possible," said Katharine Luzuriaga, a pediatrician and HIV researcher at the University of Massachusetts. "It is 100% obvious and imperative" that trials should be done in both populations," said Arvin.

Do the usual rules apply?

The meeting started with discussions acknowledging important scientific gaps. Relatively little is known about how, and how well, the neonatal immune system can respond even to common childhood pathogens or vaccines. Despite a new generation of T-cell assays that can quantitate cellular responses precisely (see *IAVI Report*, Dec. 2000-Jan. 2001, p.1) there has been little interest, or funding, for going back to look at how any licensed vaccines actually work. As a result, said John Sullivan of the University of Massachusetts, "we know more about HIV-specific cell-mediated immunity in infants than we do about any other disease."

One challenge in devising a vaccine strategy for infants of HIV-positive women is that exposure and infection can occur in the womb. Yet despite this *in utero* exposure to viral proteins and particles, the majority of these babies are born HIV-negative, for reasons that are not well-understood (see *IAVI Report*, July-Sep. 2001, p.4).

Glenda Gray (Chris Hani Baragwanath Hospital, Johannesburg) discussed some new clues, presenting data from a recent paper showing that the presence of Env-specific T-helper responses in cord blood correlates with protection from intrapartum and breastfeeding infection (*AIDS* 2001;15:1). Other researchers, including Sarah Rowland-Jones (*Lancet* 1993;341: 860) have also found HIV-specific cellular responses in exposed, uninfected infants.

Another perspective came from Katharine Luzuriaga and John Sullivan, who described a new study of CD8+ CTL responses in 17 HIV-infected infants before and after the initiation of HAART (*J. Immunol.* 2001;167: 7134). Prior to HAART, only 2/13 infants had detectable HIV-specific responses; in contrast, three infants co-infected with HIV-1 and CMV had detectable CD8 responses to CMV at all time points (1-23 months), but none to HIV. This could be due to differences in viral presentation *in utero*. Or, as the researchers suggest, there could be an HIV-specific effect on the CD8+ T-cells needed to fight off infection, or on the

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◀ **PEDIATRIC AIDS VACCINES** *continued from 11*

immune signals that call them to action.

In addition to virus-related effects, there are inherent limitations due to the immaturity of the neonatal immune system. Luzuriaga and others have shown that infants who start HAART before six months of age and achieve complete viral suppression lose all signs of HIV-specific immune responses, while infants who begin HAART after six months retain these responses. As meeting participant Bruce Walker (Harvard University) pointed out, the loss of these responses in the youngest infants, who are often acutely affected at delivery, contrasts with the finding that many adults treated during acute infection maintain detectable HIV-specific immune responses.

The possibility of an HIV-specific rift in the fabric of early immunity poses another set of challenges for vaccine developers. Not only will a pediatric HIV vaccine have to overcome possible immune deficiencies from viral exposure, it should also elicit protective responses from an immune system in the early stages of development—the sooner the better, since transmission via breast milk seems to be highest in the first six weeks after birth.

> "Even in the first months of life, the neonatal immune system is capable of robust responses to some vaccines."

For many diseases, babies' early immunity comes from maternal antibodies in breast milk, which has evolved to provide this protection. But these maternal antibodies are generally useless against HIV. Yvonne Bryson (UCLA Medical Center, Los Angeles) reviewed data showing that, in most cases, maternal antibodies to HIV do not neutralize the infant's virus. She also said that infants without neutralizing antibody from their mothers lack their own HIV-specific responses and progress rapidly to AIDS.

Yet when maternal antibody *does* neutralize the infant's virus, Bryson added, this correlates with lower viral load in the baby's blood. These findings echo earlier results from macaques (Ruprecht, *Transfus. Clin. Biol.* 2001;8:350, and Mascola, *J. Infect. Dis.* 1998;177: 1230) showing that passive transfer of certain monoclonal antibody cocktails protects some neonates against mucosal challenge.

Nonetheless, it is highly unlikely that vaccines alone could protect newborns right from birth. So they will most likely be tested in combination with another anti-HIV intervention given early on, such as antiretroviral therapy or antibody cocktails, that can protect infants until HIV immune responses kick in.

Having laid out the pieces of the puzzle, the participants acknowledged that pediatric HIV infection does not seem to behave like other perinatally transmitted viruses, such as CMV or hepatitis B. As Luzuriaga showed, CMV induces strong immune responses in very young infants. Infection of newborns with hepatitis B (HBV) happens almost exclusively during labor; treatment with antibody (HbIg) plus hepatitis B vaccine effectively prevents chronic infection in about 85% of these infants.

The evidence for HIV-specific T-helper responses in uninfected infants is also confounding. "It has not been reported for any other pathogen that the infant is born with immunity and yet has no evidence of infection at some point in postnatal life," says Ann Arvin. The lack of precedent is one reason Arvin and others are skeptical about the reported association with protection.

Without clear parallels in other models, researchers stressed the need for HIV studies on pairs of maternal and infant cord blood samples. That could help settle key questions, such as whether the CD4 T-cells detected in the South African study are made by mother or baby. Also needed are neonatal cohorts for examining why some infants respond better to antiretroviral treatment than others, and what factors influence infants' HIV vulnerability and protection. "Without such studies, we are never going to know the numerator or the denominator for how many kids make immune responses and under what conditions," said Gray.

What are the models?

Is HIV following different rules? Or have we failed to understand the rules as they are? Bruce Walker posed this question as the meeting segued into a discussion of other models. However imperfect such comparisons may be, studies of proven vaccines may help reveal what types of immune responses are generated after birth, and how quickly.

Ann Arvin and her colleague Hayley Gans (Stanford University) reviewed their studies of measles vaccines, providing an in-depth picture of humoral, cellular and cytokine responses in 248 infants immunized at six (n=93), nine (n=77) and 12 (n=78) months. In their studies, younger babies received live measles or mumps vaccine at six and nine months of age, followed by live-attenuated measles-mumps-rubella (MMR-II) vaccine at 12 months; babies enrolled at 12-months or older received a single dose of MMR-II.

All infants showed robust measles-specific T-helper responses, as measured by T-cell proliferation and interferon-gamma production assays 12 weeks after vaccination. That applied equally to babies with maternal antibody, contradicting the dogma that maternal antibody interferes with vaccine response—perhaps by "soaking up" vaccine antigen.

However, the findings differed for antibody responses. Using a level of 120 μIU (milli-international units) of neutralizing antibody—the threshold previously correlated with protection against measles—Arvin and Gans found that only 36% of the 6-month old infants showed this response, compared to 100% of 9- and 12-month-olds. No differences were seen between 6-month old children of unvaccinated versus measles-vaccinated mothers (who lack or have low levels of measles antibody), again contradicting the idea that mater-

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AIDS Vaccines 2001: Meeting Briefs

BY RICHARD JEFFERYS

One of the field's major new meetings, "AIDS Vaccine 2001" was held in Philadelphia on 5-8 September 2001 and attracted a crowd of over 1,000 attendees. Co-sponsored by several US NIH entities together with UNAIDS, the US CDC and the French ANRS, the conference featured a packed program on topics ranging from vaccine design and basic virology to plans for clinical trials. Here we present selected scientific highlights; for coverage of Phase III vaccine trials, see the reports on pages 3-5 and 14.

Long Term Follow-Up: DNA + IL-2 Vaccine

Last year, Dan Barouch, Norman Letvin and colleagues at Harvard helped dispel some of the pessimism surrounding AIDS vaccines when they published encouraging results from a study of vaccinated macaques (*Science* 2000;290:486). In Philadelphia, Barouch presented longer-term follow-up data from these experiments (600 days, compared with the original 140), which are evaluating protection by an HIV-DNA vaccine given with IL-2 (a cytokine that enhances T-cell responses) in animals challenged with the pathogenic HIV/SIV chimera SHIV89.6P.

All four macaques given the HIV-DNA/IL-2 plasmid continued to preserve their CD4 counts and control viral replication. One animal given DNA plus IL2 protein had a late breakthrough of viremia after 300 days, with a decline in CD4 count and onset of simian AIDS. [*Note added in proof: This proved to be due to a single mutation in HIV-*gag*; see* Nature *2002;415:335 and article at www.aidsinfonyc.org/tag*]. Two animals that received the DNA vaccines alone developed signs of AIDS during this time period, and one of these animals died at day 500 after challenge. In contrast, four of eight control monkeys died within the initial 140 days, and two additional control animals died by day 500 after challenge.

Searching for correlates of continued viral load control, preservation of CD4 counts and clinical health, the researchers found that proliferative responses to SIV-Gag were the strongest predictor (with the highly significant p value of 0.0001), suggesting that T-cell help is crucial for long-term control of viremia in this model.

Some researchers have criticized the use of SHIV89.6P as a challenge virus based on the suspicion that, once initially controlled, the virus is unlikely to rebound and cause disease (though Barouch mentioned two cases of late progression in his talk, which represented longer follow-up than previously reported). These criticisms were aired publicly in a much talked-about *Newsday* article by Laurie Garrett, published on the first day of the Philadelphia conference.(http://www.aegis.com/news/newsday/2001/nd010901.html). Countering the argument that SHIV89.6P is "too easy" to protect against, Barouch also presented 600-day follow-up data from a previously published study (*J. Virol.* 2000;74:7485) showing similar control of viral loads in *gag*-DNA vaccinated monkeys challenged with SIV-E660, a strain which induces a more AIDS-like disease and which many researchers consider a more stringent challenge. To shed further light on this issue, researchers at Merck are collaborating with Letvin to test the ability of their DNA/adenovirus-based vaccine to protect against several different challenge viruses.

Based on these findings, Barouch, Letvin and colleagues are now moving the DNA/IL-2 plasmid vaccine into human studies. NIH-sponsored Phase I trials are planned through the HIV Vaccine Trials Network (HVTN 044) and the Vaccine Research Center (VRC 003). Dose-escalation protocols will examine the safety, tolerability and immunogenicity of the DNA/IL-2 construct. (The cytokine is approved for use in treating renal carcinoma, but in protein rather than DNA plasmid form.)

DNA+MVA Studies

Harriet Robinson (Emory University, Atlanta) gave an update on another DNA-based vaccine approach moving towards clinical trials. In a widely publicized study published in early 2001 (*Science* 2001;292:69), Robinson, Bernard Moss (NIAID) and colleagues analyzed a prime-boost combination designed to induce the broadest possible T-cell responses: a DNA construct containing eight viral genes (SIV *gag, pol, vif, vpx* and *vpr* and HIV-1 *env, tat* and *rev*) and an MVA vector (modified vaccinia virus Ankara strain) with HIV *env* and SIV-*gag* and *pol*. Monkeys were divided into four groups of six animals each, plus four controls, and immunized with DNA at different doses and routes, then boosted with MVA at 24 weeks and challenged mucosally with SHIV89.6P seven months later.

Presenting a more detailed ELISPOT analysis of pre-challenge T-cell responses than appeared in the published paper, Robinson reported that, on average, the macaques responded to one CD4 T-cell epitope per 105 amino acids of vaccine-encoded protein, and one CD8 epitope per 238 amino acids. She also observed that "if we had truncated any portion of our Gag-Pol construct we would have compromised the ability of some animals to mount a T-cell response."

Follow-up is now out to one year post-challenge, and all animals in the high-dose DNA and low dose i.d. DNA groups remain healthy, maintain high CD4 counts and are controlling viral load to around 1,000 copies or less. One animal in the low-dose i.m. DNA group progressed to AIDS and died since the *Science* paper appeared, while the other five remain healthy. Control animals all showed precipitous declines in CD4 counts, and three of the four died by 23 weeks.

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◀**AIDS VACCINES 2001** *continued from 13*

Robinson and colleagues have also investigated the importance of including *env* in the DNA/MVA vaccines. Using the same immunization and challenge schedule, an additional group of 12 animals was given vaccine lacking *env* and two more animals were added to the controls. Four of the 12 failed to effectively control viral load, and all 12 showed CD4 declines after challenge; CD4 counts later showed a partial recovery but achieved pre-challenge levels in only one of the 12 animals. Viral loads have remained high in the four animals that failed to control virus. One of the two additional controls has succumbed to AIDS. Robinson noted that the absence of *env* did not affect T-cell responses to Gag.

Lastly, working with Moss's group and Janet McNicholl's laboratory (CDC, Atlanta), the researchers tested whether a gp120 boost given twice (with the second DNA and the rMVA inoculations) enhanced protection. Perhaps surprisingly, they found that, whereas all eight of the non-gp120-boosted animals controlled the challenge virus, three of eight gp120-boosted animals did not. While the gp120 boosts raised pre-challenge antibody responses as measured by ELISA, they did not increase the levels of post-challenge ELISA or neutralizing antibodies.

Preparations are now underway for moving into Phase I clinical trials. Robinson's group is preparing a DNA vaccine that includes HIV-1 (subtype B) *gag, pol, env, vpu, tat* and *rev*, while Moss's laboratory is producing a matched rMVA booster with *gag, pol* and *env*. Both are expected to enter Phase I trials through the HVTN in 2002. In addition, a collaborative project with Sal Butera, Dennis Ellenberger and John Nkengasong of the CDC is developing multi-protein DNA and MVA vaccines based on subtype AG isolates from the Ivory Coast, where the CDC Project Retro-CI has HIV laboratory facilities that could support future clinical trials. The Ivoirian government has expressed interest in helping to test promising candidate vaccines.

Building a Consensus

Bette Korber from Los Alamos National Laboratory took the audience on a whirlwind tour through a forest of HIV-1 genetic trees, stopping along the way to raise points relevant to vaccine design. Looking first at the variability of HIV proteins across clades, Korber pointed out that some of them are highly conserved, including integrase, p24, reverse transcriptase and protease. This relative conservation appears linked to the number and location of T-cell epitopes within the protein: these proteins have epitopes distributed throughout, while the more variable HIV proteins (e.g., Env, Nef and p17) tend to have epitopes clustered in the least variable regions. Another factor influencing the location of T-cell epitopes is the presence of certain amino acids that fit poorly into the C-terminal F pocket of class I HLA molecules. Patterns such as these allow immunogenic regions to be predicted, with Korber's methodology identifying 9 of 11 known epitopes in Rev, Tat and Vif.

Hypothesizing that these epitope-rich regions may be critical to include in vaccine constructs, Korber also discussed how to select vaccine strains that achieve the broadest possible compatibility

HVTN PLANS FOR PHASE III PRIME-BOOST TRIAL

As Thailand prepares for Phase III testing of a prime-boost vaccine strategy in 2002 (see page 4), the US HIV Vaccine Trials Network (HVTN) is developing efficacy trial plans for a similar canarypox-gp120 combination starting in 2003. In Philadelphia, Susan Buchbinder (San Francisco Department of Public Health), HVTN protocol co-chair, described the HVTN study, its differences to the Thai trial in terms of design, goals, study population and the vaccine itself, and the ongoing process for what could be a controversial decision on whether to move forward.

The HVTN trial will use Aventis Pasteur's vCP1452, a later-generation HIV-canarypox vaccine based on subtype B (the predominant subtype in the Americas, where the trial will take place) and containing HIV env, gag and pol (as in the clade E-based Thai study), plus additional T-cell epitopes from nef and pol. The three-arm trial will test vCP1452 with and without a boost of VaxGen's gp120 subunit (clade B) in an 11,000-person cohort, and also includes a placebo arm (3:3:2 ratio). Beyond looking for protection against HIV infection or disease, volunteers will be monitored for vaccine-induced immune responses and, in those who become infected, for viral load in blood and genital secretions. The goal: to establish correlates of protection, even if the vaccine(s) proves to have only very low (10-20%) efficacy.

Success on that front—which would be an enormous boon for design and evaluation of future AIDS vaccine candidates—will depend largely on having enough statistical power built into the trial. That, in turn, has driven the setting of specific immunogenicity criteria by which the go-no go decision will be made, based on results of a just-completed Phase II trial (HVTN 203) with 330 volunteers. Buchbinder spelled these out: 36% of vaccinees showing HIV-specific CD8+ cytotoxic T-lymphocytes (CTL) at day 182, or 47% at either day 98 or day 182.

Another key factor in the impending decision is finding appropriate study populations, as well as committed investigators and governments in countries where HIV subtype B predominates. The plan is to enroll high-risk heterosexuals and men who have sex with men, both from high-enough incidence populations that trial endpoints can be evaluated separately for these two groups. So far, numerous HVTN sites in the US are on board, along with those in Peru, Brazil, Haiti and Trinidad and Tobago. Other potential sites across the Americas are now being evaluated.

In the early months of 2002, HVTN investigators and scientists at the National Institute of Allergy and Infectious Disease will be looking at the Phase II data and making their decision. Some outside researchers question the merits of going forward, especially with two trials, while others see useful differences in the two approaches, provided that ongoing discussions on pooling and comparing data pan out. Watch this space.

—P.K.

across clades. Focusing on epitope-rich regions among clade C HIV-1 isolates, her team asked whether it is better to base vaccines on consensus sequences derived from multiple clade C isolates or on a single "reference strain." They found that the difference between any two reference strains is typically twice as large as that between a consensus sequence and any one reference strain (usually around 5%). Studying multiple subtype C isolates, Korber also reported that, for the epitope-rich regions, picking consensus sequences originating in a specific country (e.g., Botswana, Brazil, South Africa or India) had only a marginal effect on divergence from the overall clade C consensus sequence. The important implication is that designing vaccines from a single reference strain may be far less effective than using a consensus sequence either for that country or for the entire clade.

Looking at the issue of cross-clade compatibility, Korber compared key sites within Gag and Env (where cleavage into class I epitopes occurs). The encouraging results: a good correlation between clade B and C sequences, an even better one among clade C reference strains; and closer again between clade C consensus sequences and reference strains. In contrast, Korber predicted that clade B and C envelope proteins may have different folding (and therefore antigenic) properties, which argues for using clade-specific immunogens when aiming to induce antibody responses.

DNA Vaccines, Genetic Adjuvants in a Baboon Vaccine Model

Chris Locher (University of California at San Francisco) reported on a DNA vaccine produced by Vical, Inc. and tested in a novel baboon (Papio cynocephalus hamadryas) model. The challenge virus was an HIV-2 isolate that causes AIDS in this monkey species over 3-7 years, derived from a West African individual with symptomatic HIV-2 infection and passaged just once in baboons. Locher's DNA vaccine construct encodes HIV-2 *tat, nef,* p55-*gag,* and gp140 *env,* with or without additional genetic adjuvants (1 mg of DNA encoding the cytokine GM-CSF and the co-stimulatory molecule B7-2). GM-CSF is thought to mobilize antigen-presenting dendritic cells, while B7-2 interacts with the CD28 molecule on T-cells to enhance activation.

The investigators immunized four animals with HIV-DNA alone and four with HIV-DNA plus genetic adjuvants, while two controls received an empty DNA vector and two received adjuvants only. Immunizations were given at months 0, 1, 2 and 6 via multiple routes (i.m., i.d. and intranasally using an Accuspray device), and baboons were challenged vaginally one month later with 100 baboon infectious doses (BID) of HIV-2.

Based on still-limited post-challenge data, Locher found that addition of genetic adjuvants to the vaccine enhanced virus-specific cytotoxic T-lymphocyte (CTL) activity compared to DNA alone, particularly in the CD4+ T-cell population. (Virus-specific CD4+ CTLs have been reported for several human viruses, including herpes simplex, Epstein-Barr and HIV; see *J. Virol.* 2001;75:9771). All four animals in the vaccine plus adjuvant group, and one given DNA vaccine alone, cleared the infection within three weeks, while HIV-2 DNA remained detectable in all control animals. Monitoring of CD4 counts and signs of disease progression is continuing.

Exposed, Uninfected IDU Cohort

George Makedonas from McGill University (Montreal) reported on a small cohort of HIV-exposed but uninfected individuals whose risk factor is injection drug use (IDU). Twenty-eight individuals with documented exposures to HIV (through needle sharing with a positive partner or partners) were enrolled. Eighteen individuals were persistently seronegative (group 1) while ten seroconverted within three months of study entry (group 2). Analysis of blood samples taken prior to seroconversion revealed that none of the individuals in group 2 showed evidence of HIV-specific CD8 T-cells (as measured by ELISPOT), similar to a low-risk control group. In contrast, 12/18 individuals from group 1 had T-cell responses to one or more class I-restricted HIV peptide(s). Follow-up of 11 volunteers is continuing (ranging from 84-722 days thus far); despite an average of eight new exposures to HIV (range 1-50), no seroconversions have occurred.

Monoclonal Antibody Protection

Dennis Burton (Scripps Institute, La Jolla) reviewed data that might illuminate ways to enhance antibody-mediated defenses against HIV. The study built on previous findings that treatment of monkeys with rare monoclonal antibodies capable of neutralizing HIV can offer dose-dependent protection against vaginal challenge (*J. Virol.* 2001;75:8340). Analyzing the data, Burton calculated that antibody titers on the order of 1:400 were required to achieve complete neutralization of the challenge virus and full protection. But Burton pointed out the unlikelihood that even effective, licensed vaccines achieve such complete neutralization, since a "good" antibody titer is typically considered to be 1:40. So he speculated that these vaccines work at less-than-optimal neutralizing antibody titers because they also stimulate cellular immune responses—a "major unknown," he said, and a subject of ongoing studies in his group.

Burton has also studied the molecular structure of the b12 antibody to elucidate how it interacts with HIV. The work has revealed a long "finger-like" structure that extends into the CD4 binding site of gp120, overcoming the notorious inaccessibility of this region to antibodies. The next challenge is to design an immunogen that incorporates this structural information and might induce antibodies which mimic b12's neutralizing capabilities. ◆

industry INSIDER

PowderJect Awarded US$ 1 Million DNA Vaccine Grant

In October 2001, the US National Institute of Allergy and Infectious Diseases awarded a US$ 1 million grant to PowderJect Pharmaceuticals, Plc (Oxford, UK), and its Wisconsin-based subsidiary PowderJect Vaccines, Inc., to spur development of a powdered DNA HIV vaccine in collaboration with Michael Murphy-Corb's team at the University of Pittsburgh.

PowderJect has developed technologies for producing DNA vaccines administered with a needle-free system that delivers them into the immune cell-rich epidermal skin layer. The company says that the system's high efficiency of delivering DNA intracellularly makes possible the use of lower vaccine doses, as well as less adjuvant (which could reduce or eliminate the high reactogenicity that has kept some promising new adjuvants from being usable). It also eliminates the risks of HIV spread through needle re-use, contamination during disposal or accidental needle sticks to health care providers.

The technology is being used to produce candidate DNA vaccines against several diseases. The most advanced is a hepatitis B vaccine under development in collaboration with GlaxoSmithKline, now in early human testing.

Merck Teams with HVTN on Vaccine Testing

On 20 December, the US National Institute for Allergy and Infectious Diseases (NIAID) announced an agreement with Merck and Co. for the company's candidate HIV vaccines to be tested through NIAID's HIV Vaccine Trials Network (HVTN). The HVTN encompasses 12 trial sites within the US and 13 outside the country. Merck will continue its own clinical testing of the vaccines, which began in 1999 and now includes several ongoing Phase I trials in both HIV-negative and positive people (the latter for eventual therapeutic vaccination).

Merck is developing HIV vaccines based both on naked DNA (plus adjuvant) and on a replication-defective adenovirus-5 vector. The present candidates contain only HIV-*gag*, but the company plans to add *pol* and *nef* to the next generation of vaccines (see *IAVI Report*, Feb.-Mar. 2001, page 1).

VaxGen Appoints New Chief Executive Officer

Lance K. Gordon has been named Chief Executive Officer of VaxGen, Inc., taking the position formerly held by Robert C. Nowinski, who left in December 2000. VaxGen president Don Francis had assumed CEO duties on an interim basis. Prior to joining VaxGen, Gordon served as CEO of two vaccine companies—Oravax, which developed several bacterial and viral vaccines during his tenure, and North American Vaccines, where he brought a new whooping cough vaccine to licensure. Earlier, while at Connaught, he led development of several childhood vaccines, including the ProHibit® bacterial conjugate vaccine against infant meningitis.

Dutch Vaccine Company Crucell Hires Two Researchers

Two well-known vaccine scientists have taken key posts with the expanding Dutch vaccine company Crucell. Virologist Jaap Goudsmit will head the company's vaccine program (to include development of vaccines against emerging and childhood infections) and become an advisory member of Crucell's executive committee. Influenza expert Toon Stegmann will be in charge of the program on childhood preventive vaccines.

Goudsmit's involvement with HIV dates back to the beginning of the AIDS epidemic in the Netherlands, when he and several colleagues established a cohort of HIV-infected gay men that is still going fifteen years later. He most recently served as chairman of the Research Institute for Infectious Diseases and the Institute for Science Education at the University of Amsterdam, and serves on IAVI's Board of Directors and as chair of its Scientific Advisory Committee. He is also a key player in the European AIDS Vaccine consortium called EuroVac. Stegmann's research has focused on mechanisms of membrane fusion employed by influenza virus. He comes to Crucell from a professorship at the Paul Sabatier/Laboratoire de Pharmacologie et de Biologie Structurale in Toulouse, France.

Crucell recently came to international attention when Merck announced it had licensed the company's human cell line expression platform (PER.C6TM) for the manufacture of their adenovirus-based HIV vaccine candidate.

Wyeth-Ayerst Developing VSV-based HIV Vaccine

Over the past several years, Yale-based investigators Nina Rose and Rose have been developing vesicular stomatitis virus (VSV) vectors for use as potential HIV vaccines. In a recent issue of the journal *Cell* (2001;106:539), Rose and colleagues present results from the first macaque experiments utilizing VSV vectors encoding HIV *env* and SIV *gag* as vaccines. Animals immunized on a prime-boost schedule involving two VSV vectors (each a different serotype) showed significant protection from CD4 T-cell loss and disease when challenged with the pathogenic SIV/HIV hybrid SHIV89.6P, with follow-up of the animals now extending out to 14 months in some cases. Preliminary data from these studies was released at the 2001 Conference on Retroviruses and Opportunistic Infections (see *IAVI Report*, Feb.-Mar. 2001, page 3).

Accompanying news of the *Cell* publication, Wyeth-Ayerst reported that they have obtained intellectual property rights to the vaccine and are conducting further animal tests prior to seeking approval for human studies.

Brazil Hosts Vaccine Meeting for Latin American AIDS Advocates

BY CRAIG MCCLURE

Leading AIDS advocates from across Latin America gathered in Sao Paulo, Brazil from 9-12 October for a skills-building and networking meeting aimed at increasing vaccine advocacy within the region's community-based AIDS movement—the first such pan-Latin American meeting. Nearly 100 people from Argentina, Brazil, Chile, Colombia, Honduras, Mexico, Peru and Venezuela attended the gathering, along with others from Spain, Canada and the US.

Organized by two of Brazil's most active AIDS NGO's (Grupo de Incentivo a Vida (GIV) and Grupo Pela Vidda/Rio de Janeiro), the meeting provided an intensive overview of AIDS vaccine development, including basic and clinical science, regional trials infrastructure, legal and ethical issues, access issues, trial participation and community involvement. Representatives from the Brazilian STD/AIDS Program, academic institutions, UNAIDS, IAVI, HVTN, and GlaxoSmithKline presented summaries of their vaccine development activities in the region. In addition, small workshops enabled participants to discuss their involvement (current and potential) in addressing vaccine issues with their constituencies.

Of the eight countries represented at the meeting, only Brazil has been an active player in AIDS vaccines, dating back to a 1994 vaccine trial conducted amid considerable controversy (see *IAVI Report*, Sept.-Oct. 1999, p. 10). But in the late 1990s—after the country's activist community successfully lobbied the government to provide free antiretroviral therapy for those who need it—Brazil again stepped up its involvement with vaccines. Today, the Hospital Escola Sao Francisco de Assis in Rio de Janeiro belongs to the US-sponsored HIV Vaccine Trials Network (HVTN) and is carrying out a Phase II trial (of a canarypox-gp120 combination); the Treatment Reference Center for STD/AIDS of Sao Paulo (CRT-DST/AIDS) will soon launch a Phase II trial of this same combination. Outside Brazil, vaccine activity is just beginning: an HVTN site has been established in Lima, Peru, and several others may be added across the region as the HVTN expands internationally and prepares for a Phase III trial at sites in the Americas, which—if it is approved—would begin in 2003 (see article, p. 14).

Throughout the meeting, wide regional disparities in access to antiretroviral therapy were a backdrop to the vaccine discussions. While Brazil has been heralded as a model of universal treatment access, achieved through its government's aggressive policies combining parallel licensing and successful negotiations with pharmaceutical companies for sharp price reductions, the majority of people living with HIV/AIDS in Latin America have no access to antiretrovirals. However, the fact that health care systems are relatively stable across the region provides a foundation for introducing these treatments—as several countries, including Argentina, Uruguay, Costa Rica and Panama are beginning to do—and for building vaccine clinical trials infrastructure.

There was broad agreement that community support for vaccine research will not be easily secured in areas of Latin America without access to antiretrovirals. Renate Koch, Executive Director of Acción Ciudadana Contra el SIDA (ACCSI) in Venezuela, noted that "one of the critical points in planning for vaccine research is access to treatment of the highest attainable standard. This cannot be subject to affordability in host countries participating in vaccine clinical trials." That view was echoed by Xiomara Sierra, who spoke of the difficulties inherent in ongoing efforts to develop an HIV Vaccine Trials Network (HVTN) site in Honduras, a country with virtually no access to antiretroviral drugs.

Several participants noted that it was the first time these issues were discussed in an official forum of Latin American activists. "The meeting made a major contribution to the community across the region towards a greater understanding of vaccine development and its implications for Latin America," said Anuar Luna from Mexico, and of the need to strengthen ties across borders.

The gathering also brought signs of deeper Brazilian commitment to AIDS vaccines, beginning with an announcement by the Ministry of Health that it will intensify its efforts on this front. "AIDS vaccine development is now a major priority of the National STD/AIDS Program," said Alexandre do Valle Menezes of Grupo Pela Vidda/Rio de Janeiro. "This could have an impact on the whole region due to the leadership role Brazil plays in AIDS policies." Another outcome, according to Ronaldo Lima of IAVI (formerly of Grupo Pela Vidda/Rio de Janeiro), is that all 50 participating Brazilian NGOs made a commitment to integrate vaccine issues into their HIV prevention programs, to include vaccine information on their websites and to link their sites to the *IAVI Call for Action* (see news item, page 18).

Although national prevalence rates are low across Latin America (only Honduras exceeds 1%), HIV is well-ensconced in certain risk groups. Male-to-male sex, heterosexual sex and injection drug use all play a significant role. In Brazil, the region's largest country, 600,000 people were living with AIDS as of December 2000 (UNAIDS). ◆

CORE IMMUNOLOGY LAB ESTABLISHED FOR IAVI-SPONSORED VACCINE TRIALS

On 13 December 2001, the International AIDS Vaccine Initiative (IAVI) and the Imperial College of Science, Technology and Medicine (UK) announced the opening of a laboratory to test and compare the immune responses elicited by the various AIDS vaccine candidates to be evaluated in clinical studies through IAVI-sponsored Vaccine Development Partnerships. The laboratory is located at Chelsea and Westminster Hospital in London, and will open to operation in January 2002.

IAVI news

Under the direction of Professor Frances Gotch, the laboratory will equip and train researchers to use ELISPOT and intracellular cytokine (ICC) assays for measuring cellular immune responses. That, in turn, should facilitate head-to-head comparisons of different vaccines as they complete early stage human trials.

"As more vaccines move forward, the questions on everyone's mind will be where should resources be focused? To know the answer, we must be confident that we have rigorously tested each vaccine and held it to the same standards," says Wayne Koff, IAVI's Senior Vice President for Research and Development.

The laboratory will train IAVI clinical trials teams in performing the assays to meet private industry and international Good Laboratory Practice standards. (Although the teams will carry out these assays at the trial sites, they will also be able to ship blood samples to the core laboratory so that critical tests of immune responses can be confirmed.) It will also provide the teams with standard equipment and reagents, including peptides and samples for assay validation, to use in the tests and to assure standard calibration. The laboratory will also catalog and store blood samples from IAVI trial sites.

The core lab research staff hope to collaborate with other vaccine developers in the future to compare the results of these assays with those of other vaccine candidates.

"CALL FOR ACTION" URGES WORLD LEADERS TO SUPPORT AIDS VACCINES

IAVI and its partner organizations are working to collect signatures on a "*Global Call for Action for AIDS Vaccines*." The petition, which can be signed at www.iavi.org/callforaction, urges world leaders to step up funding for AIDS vaccine development and to make binding commitments on financing the future purchase and delivery of vaccines for poor countries.

To date, more than 100,000 people from 145 countries have signed. The petition will be presented at the XIV International AIDS Conference in Barcelona in July 2002. Yahoo!, MSN, Viacom and RealNetworks have donated Internet advertising that link users of their sites to the petition.

THAILAND'S PHASE III TRIAL *continued from 5*

With the rate of new infections in Thailand declining steadily throughout the late 1990s, that meant looking to the country's highest-incidence regions—which led researchers to the southern province of Chon Buri, where surveillance data showed 4-6% prevalence rates (see table, page 5). The vaccine team also found very supportive staff at the district hospitals and local health centers, which became focal points for recruiting and following a cohort of 2,500 HIV-negative volunteers over 18 months for HIV incidence, risk behaviors and attitudes towards vaccine trials, while providing HIV counseling and education.

HIV prevalence at screening was 4.8%, (ranging from 3.8-7%). During follow-up, several factors were associated with higher infection risk. For men, these included low education level, IDU or recreational drug use, having tattoos, and work in temporary or unskilled jobs. Newly married women (<5 years) emerged as one of the most vulnerable groups, with other risk factors for women including two or more sex partners and an early sexual debut (age 15 or less). Having syphilis or another STD was a risk factor in both genders.

Benenson also reported that willingness to participate in a 3-year vaccine study requiring four immunizations was extremely high, with 40% of volunteers saying they would definitely participate, 21% very likely and 33% somewhat likely. Only 6% said they were unlikely or definitely unwilling to participate. There were no significant differences between men and women, suggesting that this trial could be the first Phase III study to enroll significant numbers of women. (Both ongoing VaxGen trials target predominantly male risk groups, and the cohorts are >90% male). When volunteers were asked whom they most trust for information on health, the Ministry of Public Health was very high on the list, suggesting a strong foundation for recruitment.

Follow-up rates were lower than hoped for, Benenson said, at 80% over the entire study (88% at 6 months). Loss to follow-up was most often due to volunteers moving away from the region.

Veerachai Watanaveeradej (AFRIMS) and Sodsai Tovanabutra (Chiang Mai University) reported on the surveillance of subtypes in Thailand. About 27% of infections were with non-E subtypes, mostly B, but both B/E and C/E recombinants were also identified.

The Trial Design

Based on these findings, the trial team has devised a protocol to detect 50% or more vaccine efficacy over 2-3 years of follow-up. Enrollment will target 20-30 year - olds, who showed an incidence of 0.68/100PY in the preparedness cohort, but the trial is designed around the lower figure of 0.2/100PY so it can retain statistical power even if infection rates continue to fall. Assuming a 5% loss to follow-up every six months and a two-arm trial (with half the volunteers getting vaccine and half placebo), this requires a cohort size of 15,800.

In Bangkok, Surasak Youngpairoj (Ministry of Public Health) reported that the study will build on the district hospital/ local health center infrastructure that worked well in the preparedness work, expanding it to encompass eight hospitals and the 5-10 health centers affiliated with each one. Recruitment is expected to take one year, and several measures to improve follow-up rates, especially around the issue of volunteers who relocate, will be implemented.

The trial's primary endpoint is the prevention of infection in vaccinees. Participants who become infected will be monitored for viral load and CD4 counts, and their infecting virus compared genetically with the vaccine strains. They will be referred to the public health system for care, and the US Army has committed to providing them with triple drug therapy—the official national standard, but in practice out of reach for most Thais. Blood samples will be stored for possible immunological study later on, but at present there are no plans for systematic testing of cellular immune responses or correlates of protection.

Laboratory diagnostics for the trial will be carried out by the Royal Thai Army team in a new facility, which is seeking accreditation by the American College of

Pathology—a first for the country, and the region.

Remaining Steps

Before the trial can begin, it must go through myriad approval committees, including review boards at each of the participating institutions; at Thailand's AIDS vaccine subcommittee and ethics committee; and both the US and Thai FDA. That puts pressure on Thailand to re-convene an AIDS vaccine subcommittee, which was dissolved last year amid controversy over proposals for a therapeutic vaccine trial and has yet to be reconstituted. Final agreements with the vaccine manufacturers, Aventis Pasteur and VaxGen, also remain to be formalized; although both companies say they are committed to the trial, there remain unresolved issues with VaxGen concerning workload and finances, according to its vice president for international clinical research, William Heyward. ◆

◀ **AIDS VACCINES IN ASIA** *continued from 2*

new candidate vaccines based on subtype E, the region's predominant subtype (but actually a recombinant between subtype A and a never-detected "pure" subtype E)—not to mention its emerging recombinants. With the epicenter of the epidemic now in sub-Saharan Africa, most international attention is focused on subtypes C and A. But Mahidol University's Punnee Pitisuttithum, a key figure in Thailand's vaccine effort, echoed sentiments expressed by several others when she concluded a long discussion of the country's vaccine work with the plea, "Don't forget Thailand!" ◆

◀ **PEDIATRIC AIDS VACCINES** *continued from 12*

nal antibody invariably reduces immune responses in the babies.

Perhaps the most important lesson from the measles model is that early cellular defenses are readily induced, and may provide protection before antibodies appear. "You will find so many people who say that antibodies alone protect from measles and varicella," noted Arvin. "I feel it is a gap in our thinking, because the rest of the [immune] response was never measured."

Arvin was among the many speakers who emphasized that there is probably more than one component of neonatal protection, and that the ingredients of natural protection may differ from those induced by vaccines. In her view, even vaccines that induce only some components—for example, cellular but not humoral responses—are still worthy candidates. "It seems like that child would be way better off than one who hasn't been immunized," she said.

A primate paradigm shift?

Marta Marthas (California Primate Research Center, University of California at Davis) showed preliminary data from an HIV vaccine study that looked for protective responses in neonatal macaques fed SIV orally. Eight newborn macaques were immunized at 0, 2 and 3 weeks of age with a canarypox vaccine vector (ALVAC) containing *gag*, *pol* and *env*, and nine newborns with an MVA vector containing *gag* and *pol* (0, 3 weeks). At week four, all immunized and control animals were given repeated low-dose oral challenges with SIVmac251 (three times daily for five days). By 12 weeks after challenge, 7 of the 9 MVA-immunized animals were infected (peak viremia 106-107), along with 7/8 controls (with peaks between 107 and 108)—but only 2/8 of the ALVAC group.

Differences in immunization schedules and HIV antigens in the two vaccines prevent a straightforward comparison of the approaches. But if the canarypox data hold up with larger numbers of animals, they bode well for prospects that a vaccine can induce protection in breastfeeding infants. And they may bolster arguments for the Phase III canarypox trials under consideration by a US/Thailand Army collaboration and by NIAID's HIV Vaccine Trials Network (HVTN) (see articles, pp. 4, 14).

They also suggest that different challenge routes and doses can lead to different results: Genoveffa Franchini saw no protection in macaques immunized with the same stock of the vaccine, given as a single, high-dose rectal challenge (*J. Virol.* 2002;76:292).

Moving forward

Currently, only a handful of pediatric vaccine trials are in the cards. But there are signs that times are changing: PACTG 1033 is planned as a Phase I therapeutic vaccine study to evaluate safety and immune responses of infected children on HAART to two new vaccines—one based on MVA and the other on fowlpox (both newly made by Therion Biologics) expressing genes from early infant HIV isolates. These vaccines have not yet been tested in adults, and are also slated for an adult Phase I HVTN-sponsored trial.

Despite these glimmers of hope, expanding the number of pediatric trials may not be easy, said James McNamara, chief of the Treatment Research Program at NIAID's Division of AIDS (DAIDS), who noted that history seems to be repeating itself. "We're having the same conversation we had ten years ago about therapeutics," he said. "There is the same reluctance to put these experimental agents into kids."

Yet there is also the possibility that an effective HIV vaccine could be found faster for babies than for adults. Commenting on the outcome of the therapeutic studies, says Luzuriaga, "In the early nineties, people assumed that the antiretroviral agents would have to go to adults before children. We worked hard to change that, and it turned out that children [get better results] on antiretrovirals than many adults. I think the same will be true for vaccines." ◆

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EDITOR
Patricia Kahn

FOUNDING EDITOR
David Gold

WRITERS
Emily Bass, Richard Jefferys

CONTRIBUTING WRITERS
Jean-Louis Excler, Ian Grubb
Craig McClure

DESIGN AND LAYOUT
Stephen de Francesco

PRODUCTION
Michael Hariton

EDITORIAL ASSISTANT
Rozsa Szappanos

PRINTER
West End Graphics

FOUNDING MANAGING EDITO
Denise Gray-Felder

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vaccine BRIEFS

California Passes Landmark Legislation on AIDS Vaccines

In October 2001, California enacted a bill requiring all health maintenance organizations (HMOs) in the state to pay for any FDA-approved AIDS vaccine that becomes available. The bill is meant to provide meaningful incentives for biotechnology and pharmaceutical companies to invest in AIDS vaccine development by guaranteeing a sizable market for successful products.

Authored by Senator John Vasconcellos (Democrat, Silicon Valley), the new law justifies the bill's eventual pricetag as a savings over what insurers now pay to treat HIV-positive people with antiretroviral drugs, which cost US$ 10,000-$12,000 per person per year. California has the second highest AIDS caseload of any state in the US, with almost 16% of the nation's AIDS case burden and 8,000 new cases added each year. As of December 2001, over 48,000 Californians were living with HIV/AIDS. The system established by the bill should enable insurers to obtain favorable volume discounts from vaccine manufacturers, while allowing the manufacturers to maintain "first tier" prices.

The law is scheduled to take effect in January 2003. The full text is available at: http://info.sen.ca.gov/pub/bill/sen/sb_0401-0450/sb_446_bill_20011009_chaptered.pdf

First Trial Launched at Vaccine Research Center

The new Dale & Betty Bumpers Vaccine Research Center (VRC) on the National Institutes of Health campus in Bethesda, Maryland has launched its first clinical trial of an AIDS vaccine (01-I-0079). The Phase I study will investigate a naked DNA construct encoding the *gag* and *pol* genes from HIV-1, genetically engineered to express higher levels of *pol*–encoded proteins than the native HIV virion and thereby potentially eliciting a broader immune response.

The placebo-controlled trial is recruiting 21 HIV-negative healthy men and women, ages 18 to 60, who are at low risk for HIV infection. Volunteers will be divided into three groups of seven (5 vaccine and 2 placebo). The first group will receive 0.5 mg of vaccine DNA; the second—if there are no adverse effects in the first group—will get 1.5 mg, and the third group, 4 mg. Immunizations will be given once a month for three months using the needle-free Biojector system, which shoots vaccine through the skin into underlying muscle using compressed air. The study is expected to run for about one year after the first immunization, which was given on 6 October 2001.

Vaccine Workshop in Barcelona

A one-day workshop for NGO representatives, researchers and public health officials on accelerating efforts to develop and deliver AIDS vaccines globally will be held in Barcelona, Spain on 6 July 2002, prior to the XIV International AIDS Conference. Detailed information will be announced in the *IAVI Report* and on the IAVI website.

HIV Vaccine Trials Network Appoints Director

The HIV Vaccine Trials Network (HVTN) has announced the appointment of Judith N. Wasserheit, former director of STD prevention at the CDC, as the Network's first director. Wasserheit will serve alongside HVTN's principal investigator, Lawrence Corey from the University of Washington in Seattle. At the CDC, Wasserheit directed STD control efforts for over a decade, leading initiatives to prevent chlamydia, eliminate syphilis, and make the early treatment of STDs a routine part of HIV prevention.

The HVTN plans to launch several new HIV vaccine trials in the coming year, including tests of vaccines under development at Merck (see Industry Insider, page 16). More information can be found on the HVTN's newly redesigned website at http://www.hvtn.org.

VaxGen Phase III Trial

The ongoing US/European Phase III trial of VaxGen's gp120-based AIDS vaccine (AIDSVAX®) will continue to its scheduled completion at the end of 2002, following a review of the interim results by the Data Safety and Monitoring Board (DSMB). The company had planned to stop the trial early if the vaccine demonstrated at least 30% efficacy in preventing HIV infection, but the data accumulated so far do not support such a move. A second trial of AIDSVAX® in Thailand (see article, page 3) is set to conclude in the summer of 2003, with an interim analysis in late 2002.

In parallel, the company reports that it is moving ahead with plans for producing the vaccine on a commercial scale, in anticipation that the 30% level will be reached at the trial's end and the vaccine will be licensed. Earlier this year, VaxGen raised US$ 20 million to prepare for large-scale production and market introduction, and on 19 October, new CEO Lance Gordon (see *Industry Insider*, page 16) announced that the company has obtained land in the South Korean city of Incheon to build a manufacturing facility. The agreement provides VaxGen with about 26 acres in the new Songdo Industrial Park, free of charge for the next ten years.

WTO Declares Drug Patents "Should Not Prevent" Nations from Protecting Public Health

On 14 November 2001, the concluding day of the fourth World Trade Organization Summit in Doha, Qatar, ministers issued a declaration acknowledging that developing nations have the right to override certain drug patent protections when public health emergencies demand it. The new declaration does not reverse the patent protections of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, but recognizes the right of developing nations to produce cheaper generic medicines in times of crisis when adherence to the TRIPS agreement would prove an obstacle to protecting public health. However, the ministers deferred a decision on the key issue of parallel importing (importing drugs from countries which receive them at discount, rather than direct importing from the manufacturer) to the end of 2002, when a special council will submit its findings.