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Cent Gardes Vaccine Meeting Highlights Role of Antibodies in Protection

BY PATRICIA KAHN

From 27-29 October 2002, about 200 scientists gathered in Annecy, France for the "13th Cent Gardes Symposium on HIV and AIDS Vaccines." Meeting for the first time in this scenic Alpine town, the symposium still bears the name of its original home outside Paris—the historic building where Napoleon III once housed his elite troop of bodyguards, the "Cent Gardes," and Louis Pasteur later maintained his animal laboratories.

Aside from its new location, the conference opening featured another novelty: a welcome letter to participants from former US President Bill Clinton, expressing his strong support for increased efforts in the fight against AIDS and applauding the commitment of scientists in leading the battle.

Its scientific sessions also began on an unusual note, turning the spotlight on renewed efforts to make vaccines that induce broadly neutralizing antibodies (NAbs)—following years of discouragement about the prospects for success, and a shift of focus onto vaccines targeting cellular immunity. "Neutralizing antibodies are coming out of the shadows, where they've been for the past several years," said Susan Zolla-Pazner (New York University), who chaired the first NAb session. In addition, the conference featured updates on the widening pipeline of vaccine candidates and continuing studies on how to best induce cellular immunity, concluding with a sobering session on the enormous challenges still ahead in conducting large-scale trials in developing countries where the epidemic is raging.

The "Comeback" of Neutralizing Antibodies

The renewed focus on antibodies comes at a time of growing awareness that HIV vaccines based on cellular immunity alone will, at best, protect against disease—not infection—and may work for only a limited duration. The hope is that vaccines which induce antibodies capable of neutralizing diverse primary HIV strains will go further, by blunting or completely preventing initial infection. But the field has long been at an impasse in designing such immunogens, with those developed so far inducing only NAbs of narrow strain specificity.

However, two developments in the past few years have fueled a sense that the problem is solvable and that NAbs may indeed bring some of the hoped-for benefits. First was the isolation of rare human antibodies (as monoclonal antibodies, or MAbs) that target conserved epitopes of the HIV envelope protein (Env) and show broad neutralizing ability, proving that the human immune system *can* produce such Abs. Second was the demonstration, initially by the groups of Ruth Ruprecht (Harvard Medical School, Boston) and John Mascola (Vaccine Research Center, Bethesda), that passive immunization of macaques with cocktails of these MAbs can protect against subsequent challenge with pathogenic SHIVs.

At Cent Gardes, the sessions on NAbs gave an excellent overview of how the field is attempting to build on these findings, and of the overall state-of-the-art.

Neutralizing Antibodies in HIV Infection

The talks began with a presentation by George Shaw (University of Alabama, Birmingham) on the role of NAbs in controlling HIV dur-

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ing infection, and at how virus manages to evade these immune responses. Describing a study that followed 20 people for two years from the time of acute infection, Shaw reported that all 20 made NAbs (detectable in the first patients at about 10 weeks) which were initially very effective in neutralizing the patients' own (autologous) virus. But over time, the early viral population lost its sensitivity to neutralization and was eventually replaced by completely neutralization-resistant strains—suggesting that NAbs exert strong selective pressure during infection, and play an under-recognized role in suppressing viral replication.

Analyzing the sequence changes in Env to determine how this resistance arose, Shaw found that only 4 of the 15 most common mutations fell within known neutralizing epitopes—in contrast to HIV escape from cellular immune responses, which usually reflects mutations in epitopes targeted by the responding CD8 T-cells. Instead, 7 of the 15 mutations were at glycosylation sites—suggesting that HIV often escapes from antibodies by modifying its already-dense "glycan shield" to better obstruct NAb binding. Site-specific mutagenesis studies of Env supported this model: by changing amino acids known to bind carbohydrates, viral resistance to neutralization could be increased up to 100-fold.

Similar findings were presented by Doug Richman (VA San Diego Healthcare System), who also followed NAb responses and Env sequence evolution in infected people over time. In his study, 12/14 patients had substantial NAb titers to autologous virus starting at about week 8—but by one year virus had escaped from these NAbs, which showed poor recognition of HIV strains other than the initial one (even those from the same clade).

But Richman closed on a more optimistic note, pointing out that HIV's apparent ease in evading NAb responses might not extend to vaccine scenarios. In a vaccinated person, the immune system would have a head-start following exposure to HIV; without vaccine, it starts from behind and must play catch-up with the rapidly-replicating virus.

Passive Immunization and Protection by NAbs

Several speakers presented work looking more closely at passive protection of macaques by broadly neutralizing antibodies. Harvard's Ruth Ruprecht reported that her group's studies with cocktails of 3 or 4 neutralizing MAbs have shown protection in 22 out of 31 newborn monkeys challenged orally with pathogenic SHIV, leading her to suggest that the well-conserved epitopes targeted by these MAbs might be good candidates for inclusion in vaccines.

In a conceptually fascinating experiment, John Mascola presented a follow-up study to his earlier demonstration of passive protection via MAbs—although the results were ultimately inconclusive, given limitations on the numbers of monkeys available, and therefore on the different dosage variables that could be tested. The idea was to combine MAbs and cellular immunity, asking whether a sub-optimal MAb dose (which on its own protects some but not all animals) blocks infection completely in rhesus macaques previously immunized with a DNA vaccine known to protect against disease (derived from that made by Dan Barouch and Norman Letvin and carrying the same IL-2 and HIV-*gag* genes but a different *env*).

The experiment was done with 20 animals divided into four groups of five, given either: (1) DNA vaccine (4 immunizations) plus HIV-MAbs (2F5 and 2G12, at one-third the fully protective dose); (2) DNA vaccine plus an irrelevant MAb; (3) sham DNA plus HIV-MAbs; or (4) sham DNA plus irrelevant MAb (controls). One day after passive immunization, all animals were challenged vaginally with SHIV89.6PD. The findings: no difference in infection rates between the MAb-only and the vaccine-plus-MAb groups (both treatments protected 2/5 animals against infection), indicating that under these experimental conditions, cellular responses did not contribute to sterilizing immunity. All control and DNA-immunized animals became infected, with the latter showing robust CD8 responses and good control of both viremia and CD4 T-cell decline over 24 weeks.

But the study leaves open the larger question of whether some other combination of NAbs and cellular immunity to HIV might yield better overall protection (against either infection or disease progression) than candidates which induce only cellular responses. While a combination strategy is widely viewed as the most promising path to highly effective vaccines, the model is extremely difficult to test, says Mascola, given the existing shortages of monkeys and the large study that would be required.

Also addressing passive protection by antibodies, Malcolm Martin (National Institutes of Health, Bethesda) updated his lab's work on analyzing how much antibody, and what regimen, is needed to confer sterilizing immunity. His model uses polyclonal IgG from HIV-infected chimps (rather than MAbs) for passive immunization of pigtail macaques, and a high-dose, intravenous challenge one day later with SHIV-DH12, which carries the same Env protein as the HIV strain infecting his chimps. With this system, his group calculated that a fully protective dose corresponded to 149 mg IgG per kg body weight, or an antibody titer of 1:38 (the last dilution that

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GAVI PARTNERS GATHER TO ASSESS PROGRESS, PLAN FUTURE ACTIVITIES

BY SAUL WALKER

The Global Alliance for Vaccines and Immunization (GAVI)[1] was founded almost 3 years ago to reinvigorate basic vaccination coverage as a central element of sustainable development in poor countries. From 19-21 November 2002, over 300 participants from developing nations, donor agencies, industry and NGOs gathered for the second GAVI Partners meeting in Dakar, Senegal, to review progress, identify challenges and discuss ways forward.

The scale of the challenge they face was emphasized in a report launched at the meeting by WHO, UNICEF and the World Bank. *The State of the World's Vaccines and Immunizations*[2] estimates that vaccines save 3 million lives each year but that a further 3 million could be saved through improved vaccination coverage and better access in developing countries to a wider range of vaccines. The report highlights major inequalities in access to immunization services across the world: For example, while DTP vaccination rates average over 70% globally, in sub-Saharan Africa they reach only 53%, with some countries below 20%.

The meeting began with a strong statement of political commitment to reverse these dismal trends, with Ministers of Finance from 13 developing countries signing the "Dakar Declaration"[3]. The agreement commits signatories to continuing efforts to improve immunization in their home countries, and calls upon governments around the world to recognize that sustained vaccination efforts are "a national priority, a global concern and a shared responsibility."

In the opening plenary presentation, GAVI Executive Secretary Tore Godal reviewed the achievements of GAVI and its sister organization, the Vaccine Fund[4], which raises money and then disburses grants for vaccination programs. Since its inception, GAVI has distributed 180 million doses of vaccines (primarily Hepatitis B, DTP, HiB and yellow fever) and 200 million auto-disabling syringes, the latter to improve immunization safety by preventing re-use of injecting equipment. To date, 66 countries have had applications approved for GAVI support totalling $900 million, of which $130 million has been disbursed. As a result of these activities, GAVI estimates that over 100,000 lives have been saved.

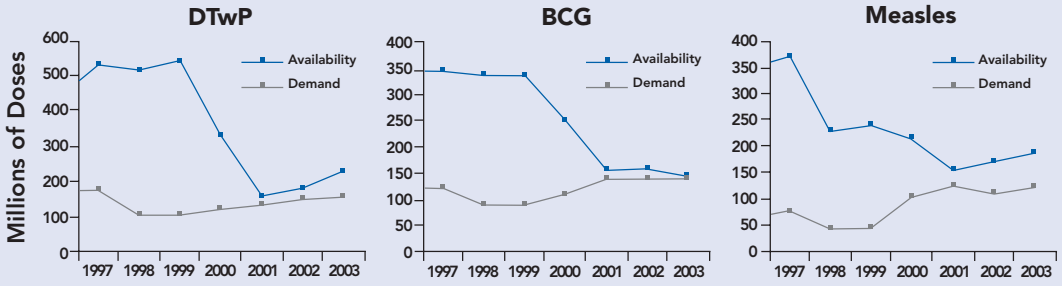
Godal emphasized that the power of vaccination to prevent disease and reduce mortality means that vaccine expenditures should be considered investments rather than costs. In this respect, he said, the world still greatly undervalues immunization as a tool for health and development.

Underscoring this point, Vaccine Fund President Jacques-François Martin pointed out that the sustainability of these efforts is far from assured: GAVI will use up all the money in its coffers by 2006, and further financial commitments are urgently required. At the same time, grantee countries and international donors must find ways to sustain the programs launched with GAVI funds, which provide a five-year catalyst grant (with the release of funds along the way dependent on vaccination milestones being achieved). GAVI is now working closely with recipient countries to develop sustainability plans for improved vaccination programs.

Ensuring Vaccine Supply

A key issue addressed both in the report and by several conference speakers is the growing difficulty in guaranteeing a sufficient, dependable supply of vaccines for developing countries. Over time, unpredictable demand, low profit margins and a move to higher-priced new vaccines in developed country markets have reduced the number of manufacturers producing basic vaccines—from 8 to 4 in the past four years, according to Carole Bellamy, UNICEF's Executive Director and Chair of GAVI's Board of Directors. So, as GAVI has successfully increased demand for vaccines, demand threatens to outstrip supply (see Figure 1)—with the result that programs for DTP and tetanus toxoid have

FIG. 1: AVAILABILITY OF THREE "TRADITIONAL" VACCINES SUPPLIED TO UNICEF



Source: Divergence of products for public sector immunization programmes. *Milstien, Julie, S. Glass, A. Batson, M. Greco and J. Berger. Presentation to the Strategic Advisory Group of Experts of WHO's Department of Vaccines and Biologicals, Montreux, 15 June 2001. www.VaccineAlliance.org/reference/ppt/sage136.ppt. DTwP contains whole-cell pertussis vaccine.*

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◀ **GAVI PARTNERS MEETING** *continued from 3*

already been scaled back for 2003, and several other programs are also in jeopardy. In view of the escalating shortage, said Bellamy, UNICEF is now reviewing its procurement policies—recognizing that pushing for for the lowest possible prices can be counter-productive in the end if it drives manufacturers out of the basic vaccines market and endangers long-term security of supply.

Manufacturers based in middle-income countries, particularly India, have increasingly stepped in to fill the gap and are now supplying the majority of basic vaccines used by developing countries. However, the few such producers pre-qualified by WHO (in terms of meeting Good Manufacturing Practice standards) still cannot reliably meet demand. Consequently, much discussion at the meeting focused on how to improve long-term forecasting of the demand for basic vaccines (against which manufacturing capacity can be scaled), increase the number of pre-qualified middle-income country manufacturers and increase industry confidence that a sufficient, predictable return can be made by producing vaccines for developing countries.

Middle-income country manufacturers at the meeting emphasized their willingness to play a bigger role, but pointed to some of the challenges they face. According to Luis Saturnino Herrera Martinez of the Developing Countries Vaccine Manufacturers' Network[5] and the Cuban vaccine manufacturer Centro de Ingeniería Genética y Biotecnología (CIGB), access to new technologies, capital investment and changing regulatory requirements are key concerns.

Building Effective Delivery Systems

The problems of ensuring that vaccines actually reach those who need them were highlighted by workshops looking closely at the logistics and realities of vaccine delivery—which account for up to 70% of the actual cost of immunization programs (see Figure 2). Stock management, transportation, cold chain maintenance, safe injection practices, record keeping and waste disposal all present major challenges in countries with minimal healthcare infrastructure or trained staff, and where numerous health demands compete for a very small pot of money. Many speakers highlighted the need for greater support at this level as essential to the success of immunization programs.

Increasing Access to New Vaccines

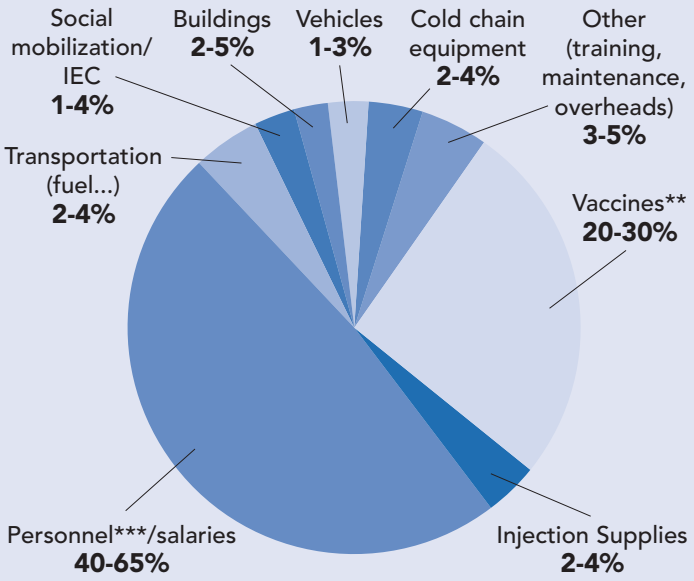
As it looks forward, GAVI hopes to play a key role in bringing not only basic childhood immunizations but also new vaccines into developing countries. To this end, GAVI has recently launched Accelerated Development and Introduction Programmes (ADIPs) that will implement strategies to develop, produce and introduce new vaccines for rotavirus and streptococcus pneumonia[6] Raj Shah of the Bill and Melinda Gates Foundation presented the ADIPs as the next stage of GAVI's role in catalyzing the continued strengthening and development of vaccination programs in developing countries.

Looking further ahead to AIDS vaccines, IAVI President Seth Berkley gave an overview of progress and challenges in the field, while a panel of speakers from GSK Bio, IAVI and the Program for Appropriate Technology in Health (PATH) considered the future challenges for HIV, TB and malaria vaccines. Panelists emphasized the importance of building a solid foundation for effective immunization programs, not only for today's vaccines but for future ones as well. Walter Vandermissen (GSK Bio) spoke for many industry participants in commenting that the world's willingness and ability to use current vaccines in developing countries are key to improving industry confidence that there will be future markets for these new vaccines. "Such confidence is essential in influencing R&D decisions today," he said. ◆

Saul Walker is IAVI's European Policy Coordinator, based in London.

1 www.vaccinealliance.org/home/index.php
2 *State of the World's Vaccines and Immunizations* WHO/ UNICEF/ World Bank, November 2002. www.who.int/vaccines-documents/DocsPDF02/www718.pdf
3 www.gaviftf.org/docs_activities/pdf/dakar_declaration_english.pdf
4 www.vaccinefund.org/en/htm/
5 www.dcvmn.org
6 www.vaccinealliance.org/home/adipad.php

FIG. 2: COST PROFILE OF IMMUNIZATION PROGRAMS*
Cost per Fully Immunized Child



** Based on a selection of in-depth developing country-specific costing studies.*
*** The share of vaccines varies, depending on different country vaccination schedules, and will be greater with the introduction of new vaccines.*
**** Personnel costs are likely to be the main cost driver of immunization programs. These costs vary across countries depending on differences in wage levels and whether shared personnel costs are included.*

Source: State of the World's Vaccines and Immunization, 2002. *A joint publication of the WHO, UNICEF and World Bank: www.who.int/vaccines-documents/DocsPDF02/www718.pdf*

Are Babies in a Blind Spot?

Pediatric Workshop Highlights Barriers to Neonatal HIV Vaccine Development

BY EMILY BASS

This October, the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) co-sponsored its second meeting on HIV vaccines and immunoprophylaxis in infants.* Held in Seattle, the 2002 gathering shared a location—and many participants—with the biannual meeting of the HIV Vaccine Trials Network (HVTN). But in spite of this neighborliness, the Glaser meeting underscored the fact that pediatric studies are still marginal to AIDS vaccine research. The last pediatric AIDS vaccine trial started in 1997 (see Table 1), and it is still the only one—out of an estimated 24 ongoing studies of preventive vaccines—which includes infants. There has never been a pediatric vaccine trial in the developing world, where there is an acute need for strategies to prevent breastmilk transmission of HIV.

Nor are there signs of imminent change. The only trials in the cards are the oft-postponed HIV Prevention Trials Network protocol (HPTN 027) for Uganda, which originated in 1999, and two protocol concepts that have been approved by the Pediatric AIDS Clinical Trials Group (PACTG). But none of these trials has an official start date, making it unlikely that they will begin before 2004 at the earliest.

Seen from a research perspective, the big news from the Seattle meeting was that there is almost no news at all. Attended by nearly 70 people, the gathering provided an unusual degree of cross-talk between pediatric researchers, pharmaceutical companies and the FDA. Unlike the 2001 meeting, which had no industry representation, this year's event was attended by most of the major vaccine companies—including Aventis Pasteur, Chiron, GlaxoSmithKline, Merck and Wyeth. However, with the exception of Aventis, which will collaborate on the 027 protocol and has worked on a similar US trial, none of the companies has plans for new pediatric studies of HIV vaccines.

Why Test HIV Vaccines in Babies?

The inaction belies an urgent need for a neonatal vaccine. Recent figures from UNICEF and UNAIDS indicate that an estimated 1,700 infants are born with HIV every day, and another 300 acquire the virus through breastmilk transmission. While there are several cheap antiretroviral regimens to help prevent in utero and intrapartum infection, there is still no completely effective way to minimize the risk of transmission via breastfeeding, which remains a common choice among women in developing countries for a variety of reasons (see *IAVI Report*, Jul-Sep 2001, p.3).

Treating HIV-positive women is one important strategy, since antiretrovirals (ARVs) would improve maternal health and reduce the amount of virus in breastmilk. This approach is being rolled out, albeit slowly, through "MTCT Plus" programs that offer medications to women and their families. But in practice, it will be many years before all women can access these drugs. Should a neonatal HIV vaccine become available, it could be added to the prevention package—and without ARVs, an immunization approach is even more important.

Despite the urgency of the problem, the current paradigm for HIV vaccine development is to push forward with adult trials and hold off on pediatric studies until a product is much farther down the testing pipeline in adults. Jeff Safrit, senior programs officer at the EGPAF and a co-organizer of the Seattle meeting, says he's been told by the HVTN and the Division of AIDS (DAIDS) that they will move into new pediatric trials "once there's a vaccine in hand and ready for Phase III trials in adults." This is due, in part, to the explicit mandate of some networks. "The hand that's been dealt [the HVTN] is adult trials," HVTN head Larry Corey told the gathering. "Our aim is to get safety and immunogenicity data to the pediatric vaccine community as soon as possible." IAVI, which currently conducts its trials exclusively in adults, is also considering pediatric trials once the adult program is further along. At the moment, VaxGen, which is poised to release data from its Phase III trials in 2003, has no plans for pediatric bridging studies if AIDSVAX shows some efficacy in adults.

Statistics aside, there are good scientific reasons for pursuing an HIV vaccine for babies. One is that it may be easier to develop a vaccine which protects infants than adults, since protection is only needed for the duration of breastfeeding. There are also examples of currently licensed vaccines—including chickenpox and flu—which are more effective in children than in adults. Put another way, if the world waits for adult efficacy before launching pediatric trials, it could inadvertently discard a worthwhile vaccine. On a practical level, global vaccine delivery sys-

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**Immunoprophylaxis for HIV-1 in Pediatrics: Moving Concepts to Reality on Vaccines and Passive Immunity.* Co-sponsored by the Elizabeth Glaser Pediatric AIDS Foundation, National Institute for Allergy and Infectious Diseases, and the Office of AIDS Research

◀**ARE BABIES IN A BLIND SPOT?** *continued from 5*

tems are set up to serve babies, not adults—so an effective HIV vaccine could probably be rolled into existing childhood immunization programs. In contrast, in many countries, adult vaccination programs will require delivery systems that have yet to be developed.

All these rationales have been forward for many years, to little or no avail. It's a difficult state of affairs—particularly to veterans of the field. Pat Fast, IAVI's Medical Affairs Director, is a pediatrician who watched the launch of the first pediatric vaccine trials in 1993 as a member of the HIV vaccine program at the National Institutes of Health (NIH). She recalls that the early studies were seen as a first step to testing candidates in developing countries, following the logic that it would encourage pediatric vaccine trials in Africa, for example, if similar studies had already been done in the US. But so far, the world has yet to take that step.

Presenters at the Seattle meeting catalogued the sources of delay. Frances Mmiro (Mulago Hospital, Kampala) and Laura Guay (Johns Hopkins University, Baltimore) each gave updates on HPTN 027, which has been delayed by indecision over whether to use a well-studied but non-clade matched vaccine—even though Uganda tested an unmatched vaccine in 2000-2001, and detected cross-reactive immune responses (XIVth International AIDS Conference, Abs. #TuOrA1226, ThPeA7081). The trial was further delayed as investigators waited for additional data from PACTG 326. The current plan is to re-submit the HPTN 027 protocol with a clade E canarypox-based vaccine (ALVAC vCP1521, another unmatched construct, which is slated for use in the planned US Army-Thai Phase III trial). Guay says that the decision to use the unmatched construct was based on vaccine availability—a clade A version of vCP1521 is being developed, but will not be ready until 2004.

Mmiro and Guay described a domino effect, where delays in US trials can topple pediatric studies in other parts of the world. It's a situation that is likely to get worse, warned University of Rochester's Colleeen Cunningham, since it is becoming increasingly difficult to enroll either HIV-positive or -negative infants in pediatric vaccine trials in the US and Europe. ARVs and the relative ease of formula feeding in these regions have slashed rates of MTCT, so very few HIV-positive babies are born there. Against this background, many parents are reluctant to enroll either HIV-negative or -positive babies in research studies. "Any expectation that a trial has to be done in babies here [in the US] before it goes elsewhere is going to be a problem," Cunningham said.

FDA regulatory requirements can also add to the delays, says Katherine Luzuriaga (University of Massachusetts, Worcester), a meeting co-organizer and principal investigator of a proposed therapeutic trial in HIV-infected, HAART-treated babies (PACTG 1033) that would test MVA- and fowlpox-based HIV vaccines. The standard FDA practice is to require "safety and immunogenicity data in relevant adult populations" before approving pediatric clinical trials. While this guideline reflects an understandable degree of caution, it is also somewhat vague about how much, and what type, of adult data

*Table 1: Pediatric Vaccine Trials—A Brief History**

PLANNED TRIALS	VACCINE
HPTN 027 Phase I preventive vaccine study in 40 Ugandan infants of HIV-infected women Protocol to be re-submitted to Ugandan regulatory authorities Q1 2003	ALVAC vCP1521 (clade E)
PACTG 1033 Phase I prime-boost therapeutic vaccine study in 16-20 US HIV-infected children on HAART Protocol approved by the PACTG; pre-clinical and adult trials to start Q2 '03; pediatric trial start date TBA	MVA (*gag, pol, env, nef, rev, tat*) + Fowlpox vaccine (*gag, pol, env, nef, rev, tat*) Both vaccines based on pediatric clade B primary isolate and manufactured by Therion Biologicals (Clade C versions planned)
Protocol #TBA Phase I study of topical, therapeutic DNA vaccine in 18 HIV-infected, HAART-treated children 3 years or older Concept protocol approved by PACTG, pending completion of adult trial in HIV-infected people; scheduled start Q1 2004	DermaVir DNA vaccine (clade B) with all HIV genes except integrase (see *IAVI Report*, Jul-Sep 2002)
ONGOING TRIALS	
PACTG 326 Phase I preventive vaccine study in uninfected infants of HIV-positive women in US	Group 1: ALVAC vCP205 (2 doses) Group 2: ALVAC vCP1452 +/- gp120 B/B
COMPLETED TRIALS	
PACTG 230 Phase I preventive vaccine study in uninfected infants of HIV-positive women in US	Group 1: SF2 gp120 (Chiron) Group 2: MN gp120 (Genentech)
PACTG 218 Phase I therapeutic vaccine study in HIV-infected infants and children in US	Group 1: SF-2 (Chiron) Group 2: gp120 (MN) protein subunits (Genentech) Group 3: gp160 (MicroGenSys)

** Not included in this table: AVEG 104, a trial of rgp120 in HIV-infected pregnant women; PACTG 185, an early passive immunization study.*

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Gathering of Regulators from Southern Africa Tackles Vaccines and Microbicides

BY ABIGAIL BING

On 18-20 November 2002, regulators and Institutional Review Board (IRB) members from 14 southern African countries met with officials from the World Health Organization (WHO), researchers, and others working on HIV vaccine and microbicide development to discuss regulatory issues in the region.* The workshop, held in Gaborone, Botswana, built on two previous WHO regulatory meetings in Geneva and Villars-sur-Ollon, Switzerland. It was the first gathering in the series to take place in Africa, and the first to focus on specific regional challenges.

The meeting was the latest response to the pressing need for greater regulatory capacity in Africa. Historically, vaccines and other health products have been primarily tested and approved in developed countries. Resource-poor countries often lack many of the decision-making groups needed to review clinical research—including ethics committees, IRBs, and data safety and monitoring boards. They also frequently lack capacity to license and approve products. Instead, introduction of new drugs and vaccines is guided by global health organizations like WHO and UNICEF and, indirectly, by regulatory decisions made in the US and Europe.

But the urgent need for strategies to quell the raging epidemic is changing this paradigm. As more clinical trials take place in resource-poor settings, countries must be able to ensure that research done within their borders is safe and ethical. Also, without independent capacity to regulate new medical products, African nations could experience significant delays in their ability to deploy HIV vaccines and microbicides once effective products are available.

These are new expectations for many African regulators. "We have had virtually no experience with testing of vaccines," said Esnart Mwape, a regulator with Zambia's Pharmacy and Poisons Board.

According to meeting co-organizer Tim Farley (WHO Department of Reproductive Health), a key question is how to ensure speed without compromising safety. In some cases, there has been relatively little scrutiny of clinical trials conducted in the developing world—for example, where privately-funded investigators may not have to submit protocols to IRBs at their home institutions. "People could come in and do trials without any sort of regulatory oversight," said Margaret Magagula (Ministry of Health and Social Welfare, Swaziland). "Government officials may be consulted and lend support for trials, but medical experts aren't [always] involved."

The meeting also revealed a need among regulators for more discussion and information about vaccine trials. Their questions ranged from basic safety concerns—such as whether trial participants could become infected through HIV vaccines and whether the use of viral vectors could produce dangerous new viruses—to issues such as liability for adverse events during trials or after licensure. Another hotly-debated point was whether or not to approve trials of HIV vaccine candidates that do not match a clade prevalent in the region.

Without clear correlates of protection or reliable animal models, regulators have limited data on which to base trial approval decisions. For vaccines that don't prevent HIV infection but work by blocking progression to AIDS, they must therefore decide on appropriate surrogate markers of efficacy (such as viral load) and on the duration of post-trial surveillance. "How do we decide when information is sufficient?" asked Dr. Ishmael Josheph of Botswana's Ministry of Health, adding that it is especially difficult to answer such questions if medical professionals from the host country were not involved in developing the trial protocol. Decisions can be even more difficult in microbicide trials, where data is drawn largely from volunteers' reports on their use of the product.

The regulators also expressed concerns about treatment of trial participants, including standard of medical care, prevention education and informed consent. Several African representatives pointed out that US-style informed consent forms, which often contain exhaustive catalogues of potential side effects and adverse events, are too long and complex for local needs.

To feel confident approving trials, many meeting participants said they would need to see safety data from trials in the country where the product was developed. "For safety I'd like to have information from the country of origin; however, for efficacy it makes sense to have [trials] done in the country where [the product] will be used," said Prof. Norman Nyazema of the University of Zimbabwe. But a requirement for testing in the country of origin could pose

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* *Scientific Guidance for Regulation of Research and Development of Microbicides and HIV Vaccines: Southern African Regional Workshop*, co-sponsored by UNDP/UNFPA/WHO/World Bank Special Programme of Research Development and Research Training in Human Reproduction, Department of Reproductive Health and Research

Bringing Vaccines to Soweto

AN INTERVIEW WITH Glenda Gray

In 2002, South African pediatrician and AIDS crusader Glenda Gray won the 2002 Nelson Mandela award for Health and Human Rights. A tireless crusader for people with HIV and AIDS, Gray, colleague James McIntyre and their teams at Chris Hani Baragwanath Hospital in Soweto, South Africa, have spent over a decade developing one of Africa's premiere clinical trials sites. Gray's group has led the field in testing interventions to prevent mother-to-child transmission, including the South African Intrapartum Nevirapine Study (SAINT) and several other large-scale trials. Her research has also provided in-depth documentation of women's life experiences, including early age of first sexual experience and high levels of sexual abuse. In recent years, Gray and her colleagues have entered the HIV vaccine field, and begun preparing for Phase I vaccine trials, as well as conducting community education and outreach for an eventual Phase III trial. Recently, Gray talked with IAVI Report Senior Writer Emily Bass about bringing vaccine research to Soweto.

Let's start with an update on the status of the vaccine trials you're involved in.

We have submitted three trials to the Medicines Control Council [MCC] for approval. One is for a clade C VEE [Venezuelan Equine Encephalitis] vaccine. Another is the Oxford/university of Nairobi/IAVI clade A MVA [Modified Vaccinia Ankara]. The third one is the Merck trial. The MCC Ethics Committee has put a hold on approval of all vaccine trials, pending a consensus on what to do about long-term treatment of people who become infected during trials.

Who will be involved in reaching that consensus?

It's not entirely clear. What we're hoping is that the national government, together with the National Ethics Committee, will convene a meeting [possibly in early- to mid-February 2003] to raise issues and concerns and then get to some kind of consensus about what is fair and reasonable. After that, hopefully they'll lift the hold on approvals.

The Soweto vaccine research team has a strong community advisory board and an ongoing "pre-trial" protocol that screens and enrolls HIV-negative individuals as potential Phase I trial volunteers. How are these groups coping with the 'hurry-up-and-wait' phenomenon?

It's difficult to know how to pace ourselves. People like to volunteer in Soweto, and we've always had an amazing response to our outreach efforts. We now have about 50 people ready to go into a vaccine trial. We've gone through at least six months of preparedness and we don't know whether to rev up or slow down. We want to go full throttle, but we're scared of having huge numbers of people in a holding pattern.

What can you do to keep the volunteers involved?

A good strategy is to use them to go out to schools or community groups, and say, "Guess what, I'm going to volunteer for a vaccine trial."

The national government in South Africa has not taken steps so far to provide ARVs. So why raise the issue in this context?

It's intriguing and surprising. At a national government level, there's ambiguity around the provision of antiretroviral therapy. At the same time, the MCC and the IRBs [Institutional Review Boards] are talking about requiring that research trials treat volunteers who have breakthrough infections with antiretrovirals. So there is a discrepancy and a disconnect.

What do you think should be done?

My first premise is that everybody who is HIV-infected and has CD4 counts below 200 deserves and should get access to treatment. There are other logistic issues, however, because we know that CD4 counts may not drop below 200 until five or 10 years after infection. And researchers can't honestly say, "I guarantee that I will be here for the next 10, 20 years [providing treatment]," because they don't know what's going to happen on that time scale.

There should be a bigger, more sustainable mechanism [than individual researchers or trials] to manage and handle the care of people who need therapy. Now, if the government provided antiretroviral therapy for all people who needed it, the problem would be moot.

Are the treatment activists paying attention to this dialogue on treatment in the context of vaccine trials?

Not really. I think they're so involved with the enormity of trying to access treatment for hundreds of thousands of infected people that they haven't really focused on breakthrough infections. However, I think they would see this debate as an opportunity to push the envelope. It comes back to the question of whose responsibility it is [to provide treatment].

What is your answer to that question?

I think it should be the researchers' responsibility, until we find a mechanism to roll out a national program.

We should be responsible for setting up the model.

Do you have a vision for that model?

We would have to work either with life insurance companies or private medical aid organizations to develop a trust fund. When people need treatment, wherever they are in the country, there can be confirmation that they were on a vaccine trial. Then the fund would release money for them to get access to treatment and monitoring.

You haven't done microbicide trials at your site, but is your sense that their approval process has been different than for vaccines?

They seem to be a lot less controversial. The interesting thing is that no one has ever bothered asking [people running those trials] about what they're going to do in the event of a breakthrough infection. I maintain that it's because microbicide trials happen in women. In fact, when I once challenged [an important decision-maker] on this issue, he said to me, "Well, you know, with vaccines you [the researcher] put something in someone's arm. With microbicides, a woman does it to herself." So if we scientists give someone an injection, that makes us more responsible? I think this reflects different ethics for different cohorts and different interventions.

Have there been trials of other [non-HIV] vaccines in Soweto?

There was a Phase III pneumococcal vaccine trial [completed in 2001] that was pretty amazing. It involved almost 40,000 children, and less than 10% were lost to follow-up. Another nice thing was that, at the time the study was done, there was no HiB [Hemophilus influenza-B] vaccine available—so they compared pneumococcal plus HiB vaccination to HiB by itself. That brought an overall therapeutic benefit to the program. The experience also showed that that the community is willing to be involved in vaccine trials and even to allow infants to take part.

What would it take in South Africa to get an HIV vaccine trial going in children?

I think these trials are plausible and feasible if we present them as a strategy to prevent mother-to-child transmission.

Do you think that pediatric trials will have to wait until efficacy trials have been done in adults?

I would hate for that to happen. Once we have data on safety and dosing in adults, we should be able to move into safety and dosing in children, adolescents and infants. It would be terrible to wait until we're halfway through an adult efficacy trial before we start studies in children and adolescents.

In your research on what's behind the high infection rate in young South African girls, you've found that some girls in Soweto are sexually active as early as age 10 [see p.15]. How are you reaching out to such young people?

We've employed an HIV-infected teenager, a 19-year-old girl, in our vaccine unit. She started having sex when she was nine years old and fell pregnant when she was 15. By then she was HIV-infected. She now goes around schools and talks about HIV/AIDS, about vaccines, about risk-reduction counseling.

Next year, we want to do surveys amongst teachers, parents and adolescents, asking the adolescents if they would they be part of a vaccine study and asking the adults if would they allow or encourage their children or students to take part, and what they think the issues are. This could give us enough data to challenge the current preference for trials only with adults in South Africa.

I've had some informal discussions with parents of 9- and 10-year-olds, asking if they would put their kids in an HIV vaccine trial. The answer is usually affirmative. I haven't met one parent who was completely appalled by the idea.

Where is the country now on the issue of clade and the importance of matching or not matching vaccines?

If there's one thing we've achieved this year in South Africa, it's that scientists in the country have agreed on the importance of going ahead with both matched and unmatched vaccines. [South Africa's heterosexual epidemic is almost exclusively clade C].

Has the clade issue contributed to delays in approving the proposed trials? [Two of the three pending protocols involve non-C vaccines.]

No, I don't think so, not at all. When we submitted the non-clade C proposals, we were very clear why we need to do them. Merck has shown that there are cross-clade immune responses to their vaccine. These findings helped push the scientific envelope in the country.

We were clear that the MVA-based vaccine [based on clade A] was from a clade common in East Africa, and that this trial is a good opportunity for further collaboration with other African scientists. Also, the Merck trial provides a chance to participate in a multinational trial, which is quite exciting.

Initially there was a push in South Africa and elsewhere for clade-matched vaccine trials. I think there was a good political and scientific rationale to push clade C vaccines, because at that stage, nobody was working on anything except clade B. By pushing C, we got a whole lot of people interested in non-B clades. But now that we've done that, let's look at the science, and at the value of testing unmatched vaccines.

If you ask us what we have achieved this year, it's that there are three vaccine trials waiting for approval—which is phenomenal. ◆

◀ **ARE BABIES IN A BLIND SPOT?** *continued from 6*

is sufficient. In the case of PACTG 1033, for instance, Luzuriaga was surprised by an FDA request for Phase I trial data in both HIV-positive and HIV-negative populations. Since the protocol proposed testing the vaccine in HIV-positive children, the investigators only anticipated a request for data in infected adults.

The FDA requirement for immunogenicity data was also questioned at the meeting. "If we all agree that there are no correlates of protection, why do we have to show immunogenicity in adults before going to infants?" asked Colleen Cunningham. Other participants agreed, pointing to examples of age-related differences in vaccine effects as they argued that it may be unreasonable to require adult immunogenicity data before moving to pediatric populations.

Another regulatory issue: the FDA perspective that each new genetic insert—for example, from a different clade—constitutes a new vaccine, even if the vector has received prior approval. In the case of MVA, there have been several Phase I trials of MVA-based HIV vaccines, both in uninfected and infected adults, while an MVA-malaria vaccine (now in Phase III adult studies in The Gambia) has also been tested in a Phase I pediatric study (see *IAVI Report*, Sep-Nov 2002, p.5). Despite this prior experience, the investigators of PACTG 1033 must submit their own portfolio of data, specific to their vaccine. And if they carry through with plans to develop a clade C version of the vaccine, they may well be required to repeat a full set of adult trials with this candidate before starting pediatric trials in the developing world. With fowlpox, the situation is more ambiguous: there is one ongoing adult trial of a fowlpox-based HIV vaccine in HIV-infected people in Australia, but there is less data so far than for MVA. Overall, the situation comes back to the need voiced by many participants: an appropriate, clearly-defined standard for safety data from other trials, which could support applications for new studies in lieu of launching completely new adult trials.

During the meeting, FDA representative Joseph Toerner was peppered with questions about data requirements under different scenarios, and with requests for a special FDA advisory committee to review the specific issues related to HIV vaccine research in children. In his talk, Toerner re-stated the FDA's standard—laid out by the International Council on Harmonization and the American Academy of Pediatrics—that adult safety and immunogenicity data with the identical candidate be collected before a pediatric trial moves forward. In a follow-up interview with the *IAVI Report*, Toerner reported that he brought feedback from Seattle to his colleagues, and that they had decided to maintain the current guidelines but to consider departures on a case-by-case basis.

Scientific Support for Infant Trials

The meeting's smattering of new data bolstered the scientific rationale for infant vaccines—and pointed at some of the outstanding questions about current animal models. Colleen Cunningham presented unpublished data from PACTG 230, a study of ALVAC vCP205 in 20 HIV-negative infants. The findings: cellular immune responses (lymphoproliferation and CTL) were similar to those seen in adults. Further insight into optimal dosage and intervals should come from final analysis of this trial and of the ongoing PACTG 326, a study comparing two slightly different canarypox-based vaccines (ALVAC vCP205 and ALVAC vCP1452), with or without a gp120 boost.

Primate researcher Marta Marthas (University of California, Davis) then presented her latest data on vaccine-induced protection of immunized infant monkeys who receive multiple, low-dose oral challenges of SIVmac251, a model that is currently the best approximation of breastfeeding exposure. Marthas has now conducted two trials of ALVAC and MVA-based vaccines, and found that both appear to protect some immunized animals against SIV infection (see Table 2). The first of these studies, presented at last year's meeting, used different immunization schedules for ALVAC and MVA; the newer study standardized the vaccination regimen, and again found evidence of protection. (The different infection rates in the 2001 and 2002 experiments are not statistically significant, according to Marthas, due to the small sample sizes; protection of ALVAC vaccinees versus controls was significant at $p<0.005$.) Interestingly, the ALVAC vector alone appeared to provide some protection. This may be a sign that general immune stimulation could improve the newborn immune system's ability to fight off disease—a theory also discussed at the last meeting.

TABLE 2: LOW-DOSE ORAL CHALLENGE FOLLOWING VACCINATION OF NEONATAL MACAQUES*

VACCINE (WEEKS OF AGE WHEN IMMUNIZED)	ANIMALS INFECTED** / TOTAL 2002	2001
None	7/8	7/8
MVA-SIVgpe weeks (0,3 in 2001; 0.2.3 in 2002	4/8	7/9
ALVAC-SIVgpe (0,2,3 weeks)	4/8	2/8
ALVAC vector alone	2/4	N/A

** data from Marta Marthas, University of California, Davis*
*** infection defined as persistent viremia (SIV in the blood) 6 months after oral challenge*

Pushing Ahead with Passive Immunization

Ruth Ruprecht (Harvard Medical School, Boston) speaking on behalf of Hoosen Coovadia (University of Natal, South Africa), presented a proposed South African protocol to test whether a cocktail of monoclonal antibodies (MAbs) to different HIV epitopes can prevent breastmilk transmission. The first phase of the study would enroll HIV-infected infants (diagnosed at birth using PCR), so that the safety profiles can be directly compared with data from a completed trial in infected adults. The babies would not receive antiretrovirals, which are not widely available in South Africa. Once safety data from the HIV-positive babies are in hand, the investigators propose a Phase Ib study in HIV-negative infants.

The rationale for this approach is that even an effective HIV vaccine given to newborns would leave them vulnerable to breastmilk transmission for the first few weeks of life, before protective immunity was established—and that passive immunization might provide "cover" during this high-risk period. Proof-of-concept studies by Ruprecht and others have shown that high doses of MAbs can protect infant monkeys against high-dose oral challenge. At the meeting, Ruprecht presented unpublished data showing that MAbs also protect when delivered up to one hour after challenge.

Laura Guay reported on a Phase I/II study of a related, relatively low-tech approach using "hyperimmune serum" made from purified antibodies from HIV-infected individuals. In a safety and dose-escalation study of one such product, called HIVIGLOB, 29 mother-infant pairs received infusions; infants were monitored for adverse events and levels of HIVIGLOB in the blood for 30 months following the infusion. This study found that HIVIGLOB was safe and well-tolerated, and had a half-life of 30 days. The study was not designed to measure efficacy, and gave the mothers and infants a single infusion of antibodies. (An earlier trial, PACTG 185, gave multiple doses to the mother, but was discontinued after the advent of AZT regimens to reduce MTCT.) The next step is to compare HIVIGLOB and short-course nevirapine (NVP) given to mother and baby with short-course NVP to both plus six weeks of NVP prophylaxis for the babies during breastfeeding. The control arm will be short-course NVP alone.

At the meeting, enthusiasm for passive immunization was mixed with skepticism about its feasibility, compared with the alternative approach of short-term, prophylactic antiretroviral therapy. MAbs might have fewer toxicities and side effects than antiretrovirals. But they have several drawbacks, including difficulty of administration compared with ARVs (they are given via intravenous infusion or intramuscular injection), the large amounts of antibody needed for protection (which translates into a high cost), and the relatively short duration of protection, which wanes as antibodies are cleared from the body. (Data from HIV-infected adults showed a half-life ranging from 7.94 days to 16.48 days for different MAbs; there is no comparable data for infants.) Another disadvantage, pointed out by Dorothy Mbori-Ngacha (University of Nairobi): many women deliver their babies outside a hospital setting, which would make it difficult to administer the infant MAb dose within 24 hours of birth. In contrast, mothers could deliver ARVs to the babies at home. Even in a passive immunization context, Mbori-Ngacha suggested that women should be given ARV prophylaxis for their infants.

A Field with No Home Base

Under the current system, advancing candidate vaccines into pediatric trials depends largely on investigator passion and tenacity. It's a selection process which does not guarantee that the best products will be tested—or that trials will go forward if the investigators move on. But there are alternatives, says Cathy Wilfert, who points out that the HPTN and PACTG could develop and advance a pediatric research agenda. A key obstacle, however, is the lack of funds: Wilfert, who chairs the HPTN perinatal working group, says that the entire US budget for the PACTG is only $30 million per year.

Despite the discouraging state of the field, the Seattle gathering nonetheless seemed to catalyze interest in these issues, with many of the industry and trial network representatives expressing enthusiasm for future collaborations—although time will tell whether this translates into concrete studies, and on what timescale. In lively discussions, participants shared diverse opinions about the best and speediest way to proceed in the times ahead. Some argued that passive immunization trials are ready to launch, and should therefore move forward. Others said that this strategy was unlikely to be practical, especially if multiple infusions are required, and that the push should be for vaccine trials. Still others proposed a trial that would compare MAbs alone, vaccine alone, MAbs plus vaccine, and ARV prophylaxis during breastfeeding.

But, while there was still no consensus at the end of the meeting, there was considerable energy for action. As Bonnie Mathieson, of the Office of AIDS Research, summed up, "We need to get one pediatric trial started as soon as possible, and start to prepare for two or three more. The time to act is now." ◆

industry INSIDER

COBRA BIOTECHNOLOGY TO MANUFACTURE SOUTH AFRICAN DNA VACCINE FOR TRIALS

In November, Cobra Biotechnology (Keele, UK) and the South African AIDS Vaccine Initiative (SAAVI) announced that Cobra will produce two DNA vaccines, developed by Carolyn Williamson's research team at the University of Cape Town, for Phase I and II trials. The vaccines encode RT, Gag, Tat, Env and Nef from clade C, and will be tested in prime-boost studies (slated for late 2003 or early 2004) with an MVA vaccine carrying the same genes.

For Phase III and commercial sale, SAAVI and Cobra will combine their technologies and jointly control manufacturing rights for the vaccine in Southern Africa. Cobra has the right of refusal to produce the vaccine for all other regions of the world. The agreement also includes a possible technology transfer of manufacturing capacity from Cobra to a South African partner.

BIOSYN AND PARTNERS RECEIVE US$10 MILLION MICROBICIDES GRANT

BioSyn (Pennsylvania, US) and five collaborating partners have received a five-year, US $10 million grant to develop a microbicide called Cyanovirin-N (CV-N). A protein isolated from blue-green algae, CV-N has shown promise in monkeys. In a study of 26 adult female macaques, 15/18 animals pre-treated with CV-N gel showed no sign of infection after challenge with SHIV89.6P, while 8/8 controls became infected (*Microbicides 2002*, Abs #A-099 http://www.itg.be/micro2002/Pages/Abstracts.html). The product showed similar efficacy in a rectal challenge study, also conducted in macaques (Abs# A-0100). CV-N is thought to work as a fusion inhibitor.

POWDERJECT PLANS PHASE I THERAPEUTIC DNA VACCINE TRIAL IN 2003

In November 2002, PowderJect, a UK-based vaccine company, announced plans for a Phase I therapeutic trial of an HIV-DNA vaccine, developed as part of a collaboration with GlaxoSmithKline (GSK). The trial will combine PowderJect's novel needle-free injection method, which delivers gold particles coated with DNA directly into skin cells, with a GSK vaccine construct. GSK will design and conduct the trial. In PowderJect's announcement, CEO Paul Dryson referred to data from a proof-of-principle experiment that the company conducted with a prototype vaccine containing a different combination of HIV-specific plasmids than will be used in the upcoming trial. The study found that this vaccine, delivered with PowderJect's technology and combined with antiretroviral therapy, can lead to control of viral load in immunized, SHIV-infected monkeys, according to Dryson. A PowderJect spokesperson said that these data are being prepared for publication.

Previously, PowderJect evaluated another DNA vaccine candidate and found that it protected 4/7 monkeys from a partially heterologous SIV challenge (*J Virol* 76:3309;2002). PowderJect is developing DNA vaccines against cancer, influenza, Hanta virus and Herpes simplex virus using its needle-free technology. It also supplies flu and smallpox vaccines delivered by traditional methods.

EPICYTE PHARMACEUTICAL AND AAI PHARMA TO DEVELOP TOPICAL MONOCLONAL ANTIBODIES IN PLANTS

In September 2002, Epicyte Pharmaceutical Inc (San Diego) announced a partnership with biotech company AAI International (a division of aaiPHARMA, North Carolina) to develop a topical formulation of monoclonal antibodies (MAbs) against Herpes simplex virus type 2 (HSV-2). Epicyte produces MAbs—called Plantibodies—through a novel technology in which antibody-producing genes are inserted into crop plants such as corn and soybeans; the antibodies are then "harvested" via a multi-step process. This process is significantly cheaper than current methods for producing MAbs. For example, the company says that the annual output of 200 acres of MAb-producing corn (estimated to cost of tens of millions of US$) would equal that of a $400 million factory using an animal cell-based system.

A topical formulation of Epicyte's anti-HSV-2 MAb, called HX-8, has shown protective efficacy in mouse studies. AAI International will develop clinical grade topical formulations for Phase I therapeutic and preventive studies of HX-8. Epicyte, which holds a broad patent covering all plant-based monoclonal antibody production (topical and systemic), is also developing anti-HIV MAbs. Phase I trials of a microbicide using these MAbs are planned for 2005.

FDA GRANTS FAST TRACK STATUS TO AIDSVAX

In December 2002, the US Food and Drug Administration granted Fast Track designation to the VaxGen's two AIDS vaccine candidates—AIDSVAX B/B and AIDSVAX B/E. Fast track status allows for rapid regulatory review upon submission of an application for licensure.

VaxGen will announce results from the North American Phase III trial of AIDSVAX B/B in the first quarter of 2003. Immediately following that announcement, the Thai Data Safety and Monitoring Board (DSMB) is slated to meet and unblind the ongoing Thai Phase III trial of AIDSVAX B/E, which began 15 months after the North America/Europe study.

FDA fast track was created in 1997 to enable accelerated consideration of applications for drugs and medical devices used against life-threatening diseases. All of the antiretroviral therapies currently in use in the United States received this accelerated approval. The fast track approval process takes approximately six months from submission of the application, but this can vary by product.

VaxGen plans to submit applications to the FDA for both AIDSVAX B/B and B/E, according to company spokesman Jim Key. However, FDA approval is not required for products that will be used only outside the US, and the B/E vaccine contains gp120 protein derived from clade E HIV—the predominant subtype in Thailand, but not in circulation in the US. Thailand has its own regulatory board, which will make its determinations about AIDSVAX B/E for in-country use, should the product be deemed efficacious and an application for licensure submitted.

◀CENT GARDES VACCINE MEETING *continued from 2*

completely blocks HIV infection of cultured cells—a more stringent criteria than that used by most HIV labs) (*J Virol* 76: 2123;2002). He also reported that IgG given six hours after challenge still blocks infection—but that by 24 hours, it's too late, although these animals controlled virus (viral RNA was first detected at week 5).

Speaking afterwards with the *IAVI Report*, Martin said that the antibody levels required to achieve sterilizing immunity in his model (with its high challenge dose and stringent route) are completely "within the range" of those attainable by vaccination, citing the example of a vaccinia-gp160 plus gp120 prime-boost regime in monkeys (*J Virol* 75:2224;2001), and are "routinely generated" in natural infection (*J Virol* 74:6935;2000). To his mind, the bigger difficulties in eliciting protective NAb by vaccination will be to get sufficiently broad responses, and whether high enough levels can be recalled fast enough when a vaccinated person is exposed to HIV.

Defining Immunogens That Induce Broad NAbs

Turning to the question of what antigens might induce potent, broad NAbs, talks ranged from studies of defined domains within Env to rational approaches towards designing new immunogens.

Focusing on a well-known antigen, Susan Zolla-Pazner argued for a new look at the long-dismissed, hypervariable V3 loop of Env as a potentially useful immunogen. While early studies in animals detected mostly type-specific NAbs to V3, antisera from HIV-infected people usually show broad anti-V3 NAbs (although these are often poor at neutralizing primary HIV strains). In re-examining V3 as a vaccine antigen, she began from the premise that it is involved in gp120 binding to CD4—which is not clade-restricted—and must therefore have some conserved features which could be exploited for vaccines. Close analysis revealed several well-conserved structural properties despite V3's hypervariable protein sequence, suggesting that NAbs which recognize 3D conformation rather than linear peptides might be more potent neutralizers of diverse primary HIV strains.

To test this idea, her group derived MAb-producing cell lines from people infected with HIV clade B or A, using a procedure to select for

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Physician-Turned-Senator Bill Frist to Lead US Senate

On 23 December 2002, Republican William Frist (Tennessee) was selected as the new US Senate majority leader, replacing Senator Trent Lott and assuming one of the most powerful positions in the US Congress. As the Senate leader, Frist will become a public spokesman and important negotiator for the party, as well as a key figure in deciding which bills are taken up for consideration by the Senate.

A former heart and lung transplant specialist, Senator Frist is the only physician in the US Congress. He has been associated with various legislative initiatives on AIDS and healthcare. During the last Congressional session, he co-sponsored the "US Leadership on AIDS Tuberculosis and Malaria Bill," (see Vaccine Briefs, p. 16), a failed attempt to authorize increased spending on these global diseases. Frist was also the Senate co-sponsor of the "Vaccines Affordability and Accessibility Act" (S.2053), a bill that sought to increase public education on and uptake of vaccines (such as hepatitis A and B) among adults and adolescents in the US, which did not pass into law. And he was the first Republican co-sponsor of the "Vaccines for the New Millennium Act" (S.895), which called for tax credits to companies working on vaccines against AIDS, TB and malaria, and for measures to help ensure access when these vaccines are licensed; the bill was not passed into law. As a member of the Senate budget committee, Frist has played an important role in setting appropriation levels for global AIDS spending, although with his new leadership responsibilities, future committee membership may be curtailed.

Some AIDS advocates greeted the news of Frist's appointment with cautious optimism. "The proof will be what he does with his leadership position," said Chris Collins, executive director of the New York-based AIDS Vaccine Advocacy Coalition. "He is clearly someone who understands the importance of vaccines and funding for AIDS. The ingredients are there for him to make a real difference."

Looking to the next Congressional session, which starts in January 2003, Collins said he would be waiting to see "what Senator Frist can accomplish on authorizations and appropriations in global AIDS and health issues" and how he will follow-up on the US Leadership bill, which came within "a hair's breadth" of passing. To revive the bill, a new version would have to be introduced and approved in both houses of Congress. But Paul Davis of the Health GAP Coalition, a group focused on US-based AIDS policy advocacy, points out that in lieu of a new version, a "presidential initiative" could be brought directly to Congress [which would have to appropriate the funds], and that "Senator Frist can use his newfound power to help ensure that this happens."

—E.B.

V3 MAbs that recognize conformational rather than linear epitopes. Data from 13 lines suggest that these MAbs do show binding and neutralization across HIV-1 clades, but not all—suggesting that V3 may exist in more than one immunologically-relevant shape.

In a very different approach he calls "reverse vaccinology," Dennis Burton (Scripps Research Institute, La Jolla) described his team's efforts to elucidate at the molecular level why certain MAbs are broadly neutralizing—by defining the epitopes they recognize and the features of those epitopes which are essential for MAb binding. The goal is to use this information as a guide in designing immunogens that might induce similar antibodies.

Burton described work on two MAbs. The first, called b12, recognizes a CD4-binding domain within Env, and detailed studies of their binding have revealed the regions, 3D shapes and probable mechanisms involved. These results, in turn, paved the way to use site-specific mutagenesis to create a gp120 immunogen that binds b12, but not epitopes for other antibodies that might divert the immune response away from the b12 epitope. Another broadly neutralizing MAb called 2G12 works in a completely different way, recognizing an epitope made of sugar residues attached to specific amino acids within Env. Structural analysis and modeling studies are being used to design an immunogen that presents sugar residues in the same way.

In terms of specific vaccine candidates targeting humoral immunity, there is little in the clinical trials pipeline other than VaxGen's gp120-based vaccines and the new GlaxoSmithKline Env-containing product. Two speakers presented new immunogens in pre-clinical development—George Lewis (Institute for Human Virology, Baltimore), who described gp120-CD4 complexes (see *IAVI Report*, Jul-Sep 2002, p. 15) and Susan Barnett (Chiron Corp, Emeryville), who discussed Chiron's native gp140 molecule (*IAVI Report*, Apr-Jun 2000, p.6). Updates on these and other NAb-inducing immunogens will be included in our reports on conferences in early 2003.

Pulling together the many different threads on NAbs, the overall sense at Cent Gardes was of a field facing enormous scientific challenges—but gaining a more solid foundation for moving forward. "We're still just teasing out a conceptual understanding of why it's so difficult to induce broad, potent NAbs, and of how to design the right immunogens," said John Mascola. "But I think it should eventually be feasible, based on the fact that potent MAbs do exist in humans."

VSV-based Vaccine Candidates

Many of the remaining talks at the meeting focused on the more familiar terrain of HIV vaccine strategies that target cellular immunity--an area where questions are much more sharply focused on evaluating specific vectors, antigens, immunization regimes and routes, both in monkeys and clinical trials.

One of the newer candidates in this category is the VSV-based candidate described by John Rose of Yale University (New Haven). VSV is a virus that infects livestock, where it a causes self-limiting infection but is not pathogenic in humans. Building on published protection data in macaques, Rose presented encouraging results from intranasal vaccination, along with studies comparing two different types of boosts.

Last year, Rose's team showed that a vaccine containing HIV *gag* and *env* in an attenuated VSV vector protected 7/7 monkeys against disease after challenge with SHIV89.6P, given 3 or 6 months after the last boost (*Cell* 106:539;2001). (The challenge and vaccine strains differed at 14 positions in Env.) All 8 control animals became infected and progressed to AIDS. After two years or more of follow-up, the 7 vaccinated animals remain healthy and continue to control virus: 6/7 have undetectable loads, while the seventh maintains a stable load of 4,000.

At Cent Gardes, Rose presented a follow-up study done at Wyeth Vaccines, which has licensed the VSV platform and is developing the HIV vaccines further. The 3-arm study looked at animals immunized intranasally (i.n.) or intramuscularly (i.m.) with VSV carrying *env*, *gag* and *pol* (3 animals per group), plus 4 controls. All monkeys were challenged 5 weeks later with the homologous SHIV89.6 strain.

Using three different assays for measuring HIV-specific CD8 T-cells (tetramer staining, Elispot, CTL killing), the researchers found that i.n. immunization consistently evoked stronger CD8 responses (about 3-fold by tetramer staining). NAb levels were similar in the i.n. and i.m. groups. But despite differences in pre-challenge CD8 responses, protection was similar in the two groups: all animals achieved undetectable viral loads and preserved their CD4 counts. However, clear vaccine-induced protection could not be shown in this study, since 3 of the 4 control animals also suppressed viremia, although not CD4 decline. (The vaccinated animals, but not controls, were all MamuA*01.)

Last, Rose described an ongoing monkey study suggesting that it is more effective to boost VSV-primed animals with a different vector. The study compares two groups of 4 animals, one boosted i.m. with a second VSV-based vaccine (carrying a glycoprotein from a different serotype but otherwise identical to the prime) and the other, an intradermal (i.d.) boost with MVA carrying the same HIV genes. The MVA boost led to higher levels of HIV-specific CD8 cells than VSV

In the next IAVI Report:

- **Do Clades Matter for Vaccines?**
- **New Data on Gender and Vaccines**
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(an average of 1.5% vs. 0.5% tetramer-positive cells, and these remained elevated five weeks later—by which time the VSV-boosted response had completely waned.

In the next phase of this NIAID-supported "vaccine development team," Wyeth is preparing for Phase I trials through the HIV Vaccine Trials Network (HVTN). Since the VSV vector replicates in humans, livestock and the cell cultures of many mammalian species, this will require extensive testing of its tissue distribution in vaccinated animals, as well as further host range and virulence testing, according to Rose. Later trials "would probably also involve a larger study in herd animals," he said. Preliminary data showed no significant pathology in 4 vaccinated cows (although the animals initially developed small lesions at the inoculation site) and no discernible pathology in 42 macaques vaccinated with VSV vectors.

Clinical Trials

Numerous vaccine candidates now in clinical trials in the US and Europe also featured heavily on the Cent Gardes agenda. These included the Merck vaccines, canarypox, GlaxoSmithKline's NefTat/gp120 combination and the lipopeptides developed as boosts through the French ANRS, all of which have been covered in recent issues of the *IAVI Report*. Gary Nabel (Vaccine Research Center, Bethesda) discussed a multi-clade DNA vaccine that just entered Phase I studies (see p.16). Another was described by Mary Marovich of the US Military HIV Research Program (Rockville), who presented a still-blinded study testing whether volunteers' own dendritic cells "loaded" with a canarypox-based vaccine construct (ALVAC vCP205) are more immunogenic than standard i.d. or i.m. immunization with the same construct. (For a complete list of ongoing vaccine trials, see poster insert, this issue, or www.iavi.org).

In the meeting's final session, speakers addressed the complexities of preparing and conducting clinical trials in developing countries (see *IAVI Report*, Jul-Sep 2002, p.2). Glenda Gray (Chris Hani Baragwanath Hospital, Soweto) spoke about the regulatory, ethical and logistical challenges facing South Africa's vaccine trial preparedness efforts, and highlighted issues arising from the fact that youth, especially young women, are at such high risk for HIV infection (see also interview, p. 8).

Gray said that about 26% of South African women who visited antenatal clinics in 2001 were HIV-infected. She also presented hard-hitting new data estimating that about 50% of South African girls are sexually active by age 15, and 10% by age 12—with coercion, violence and poverty as major factors behind these numbers (data from the Kaiser Family Foundation and South African National Youth Survey). To Gray, these findings underscore the need to greatly intensify prevention efforts in very young age groups, and to resolve issues (such as informed consent) hindering the inclusion of adolescents in vaccine cohorts . She also presented survey data from Soweto residents showing that 68% of the respondents said they were "definitely willing" to participate in a vaccine trial; 16% were "definitely not" willing, and the remainder were undecided.

Echoing many of these same themes, Pontiano Kaleebu (Uganda Virus Research Institute, Entebbe) described the strides his country has made since conducting Africa's first (NIH-sponsored) HIV vaccine trial in 1999. Through that experience, Uganda has established clear procedures for scientific, ethical and legal review of trial protocols, as well as good laboratory capacity. As it prepares to launch a DNA/MVA study in 2003, media, local community and the general public also have more knowledge, and are more accepting, of HIV vaccine trials. ◆

◀**SOUTHERN AFRICAN REGULATORS GATHERING** *continued from 7*

problems for vaccines where demand (and therefore incentive to test the product) in industrialized countries is low.

Looking ahead, participants discussed the need to prevent "brain drain" of qualified professionals away from the continent, and for regional harmonization and collaboration on common guidelines. Rubell Brewer (Sechelles Ministry of Health) called on participants to lobby their ministers to prioritize and fund regulatory structures. In addition to continuing WHO training, other suggestions included asking the Southern African Development Community Harmonization on Drug Regulation Initiative for assistance and lobbying research universities to devote resources to IRB review. The need for improved mechanisms to ensure appropriate post-marketing surveillance of product safety and efficacy was also highlighted.

"WHO can do work in this, but everyone should see their own role in this process," Ivana Knezevic (WHO Department of Vaccines and Biologicals) told the gathering. "Without your support, we won't go anywhere." ◆

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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

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vaccine BRIEFS

NEW UNAIDS DATA TRACKS MATURE AND EXPLODING EPIDEMICS

In December 2002, UNAIDS released its yearly report on the global HIV epidemic. *The State of the AIDS Epidemic 2002* (available at www.unaids.org) pairs a sobering global overview with close-up views of countries where the AIDS epidemic is expanding with horrifying speed. Overall, 42 million people are living with HIV in 2002, including 19.2 million women. Looking to emerging epidemics, the report cites China—where unchecked spread of HIV could lead to 10 million new infections by 2010—and India, where data from antenatal clinics from several states portends broader spread in the general population. The report also gives several alarming examples of the explosive epidemic in intravenous drug users (IDU). For example, in the Russian city of Togliatti, an initial survey found that 56% of IDUs were HIV-infected.

The report echoes the 2002 Barcelona Conference message that a comprehensive response to the epidemic could prevent millions of new infections, and that delaying implementation will "slash the potential gains." It also confirms the enduring gap in access to anti-HIV drugs: fewer than 4% of HIV-positive people in low- and middle-income countries were able to access antiretroviral treatment at the end of 2001.

While UNAIDS statistics are the world's most widely-cited AIDS figures, in-country data can yield divergent figures. The same week that UNAIDS released its report, the South Africa Human Sciences Research Council (HSRC) released the results of a 10,000 person study commissioned by the Nelson Mandela Children's Fund (available at www.hsrcpublishers.co.za/hiv.html.) The study estimates a national prevalence rate of 15.2% in 15-49 year olds—the UNAIDS estimate for that age range is 20.1%—and notes an "unexpectedly" high prevalence of 5.6% among 2-14 year old children. In addition to perinatal infection and early sexual initiation, sexual abuse and use of nonsterile needles could explain this high rate, authors said.

MULTI-CLADE TRIAL BEGINS AT US VACCINE RESEARCH CENTER

On 13 November 2002, the Vaccine Research Center (VRC) in Bethesda, Maryland, began Phase I studies of a "multi-clade" HIV-DNA vaccine developed in the lab of VRC director Gary Nabel. The vaccine contains *env* genes from HIV subtypes A, B and C (which together account for about 90% of all HIV infections worldwide), along with the *gag*, *pol* and *nef* genes from subtype B. The trial, designated 03-I-0022, will enroll 50 volunteers, beginning with a 2 mg dosage group (including placebos); assuming no safety problems, the next group will receive 4 mg, and the last group, 8 mg—all given in three immunizations over 56 weeks. Work is also underway to produce a second vaccine with the same HIV genes in a vector made from adenovirus-5 (Ad-5). If the DNA and Ad-5 vaccines each yield good safety and immunogenicity data in Phase I studies, they will then be tested as a prime-boost combination.

AIDS ADVOCATE BECOMES CONGRESSIONAL DEMOCRATIC LEADER

In November 2002, Nancy Pelosi (San Francisco, CA) was chosen as Democratic leader in the US House of Representatives, where the Democrat Party is currently in the minority. Pelosi is a long-time AIDS advocate who in 1999 sponsored the first legislation (the"Vaccines for the New Millennium Act") to provide incentives to companies developing AIDS, TB and malaria vaccines. This legislation was never passed into law, but there may be renewed interest in similar proposals in 2003, building on momentum from initiatives to stimulate industry involvement in vaccines against bioterror agents.

NEW HEAD FOR THE US FDA

Also in November, Mark McClellan was approved as the new Commissioner of the Food and Drug Administration (FDA), a post that has been vacant for two years. A health economist and professor at Stanford University, McClellan was generally supported by both political parties.

His appointment comes at a difficult time for the FDA. In October, the Bush Administration drew criticism for its appointment of W. David Hagar, a conservative Christian, as interim chair of the FDA panel on women's health policy. That same month, more concerns arose when the administration suspended the "pediatric rule," which allowed the FDA to require pediatric studies of products intended for widespread use in children. Recently, the institution has spoken publicly about its difficulties dealing with the volume of applications it receives.

GATES GRANT TO FIGHT AIDS IN INDIA

During a four-day trip to India in November, Microsoft CEO Bill Gates announced a US $100 million grant to combat HIV in the country's vulnerable mobile populations, including truck drivers, migrant workers and commercial sex workers. The new initiative will be overseen by a board headed by the Indian minister for Health and Family Welfare and directed by Ashok Alexander, who most recently served as head of the Delhi office of the global consulting firm McKinsey & Company.

AIDS FUNDING BILL DIES AS CONGRESSIONAL SESSION ENDS

A landmark bill that authorized substantially increased funds for HIV/AIDS, tuberculosis and malaria was dropped from consideration when the 107th session of the US Congress ended in November 2002. According to Congressional procedure, the bill—the "US Leadership Against HIV/AIDS, TB and Malaria Act of 2002"—was dropped from consideration, since it had not been enacted at the session's end. The House and Senate each passed separate versions of the bill, but work by staff to produce a reconciled version failed. The legislation called for US$5 billion in spending for global AIDS and substantial increases in US investment in micrcobicides research. No announcements have been made about whether similar legislation will be introduced when the 108th congressional session begins in January 2003. In a separate announcement, President George Bush put forward a presidential initiative that would grant US$500 million over three years to developing countries combating mother-to-child transmission.