

# IAVI REPORT

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## Geneva Overview

# Vaccines at the 12th World AIDS Conference

by David Gold

There was certainly no shortage of data at the 12th World AIDS Conference. The meeting, held on 25 June-3 July 1998 in Geneva, featured more than 5,000 abstracts and 400 oral presentations. While vaccine issues were somewhat more visible this year, for the most part they remain a side-issue at the international AIDS meetings. Moreover, the conference agenda presented few opportunities to bring together researchers and experts to discuss key challenges in the field and how to move promising vaccine approaches forward.

That said, the Geneva conference did include an array of interesting vaccine-related presentations. In this overview, we describe many of these.

### Wigzell plenary talk on vaccines

In a plenary talk on vaccines, Hans Wigzell of the Karolinska Institute provided a review of AIDS vaccine research and called for an expanded effort in both basic and clinical vaccine research.

Wigzell said that a vaccine that could protect against disease was far more likely than one that

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## Remembering Mary Lou Clements-Mann

### Loss of leading vaccine researcher, IAVI SAC member leaves large void

The tragic loss of Mary Lou Clements-Mann and her husband, AIDS and human rights pioneer Jonathan Mann, in the Swissair crash on 2 September 1998 leaves a large gap in the overall effort to develop a safe and effective AIDS vaccine.

Clements-Mann, the founding director of the Center for Immunization Research at Johns Hopkins University and a member of IAVI's Scientific Advisory Committee (SAC), was en route to Geneva to attend a series of UNAIDS vaccine-related meetings.

A passionate and tireless advocate for more rapid AIDS vaccine development and testing, Clements-Mann was also an extremely well-respected researcher. And, unlike many AIDS

researchers, she had extensive experience in the clinical evaluation of vaccines for other human diseases.

Seth Berkley, IAVI's President, noted that "Mary Lou was a distinguished vaccine researcher and cherished IAVI colleague. Jonathan was a world-renowned AIDS leader and an unyielding defender of human rights and the right to health care for people around the world. Their deaths leave a large void in the ranks of those working to control this global pandemic."

As a founding member of IAVI's SAC, Clements-Mann played a key role helping shape the Initiative's scientific program.

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could prevent infection. He also described VaxGen's plans for Phase III gp120 trials in the U.S. and Thailand as "quite reasonable." While acknowledging that breakthrough infections had occurred among gp120 recipients in Phase I and II trials, he warned that "if we don't begin now, we will never know if it will be effective."

### Emilio Emini on HIV vaccines

In his first public comments since taking over responsibility for Merck's vaccine development program, Emilio Emini shared some of his perspectives on HIV vaccine research.

Merck's program, Emini suggested, will focus on generating potent cytotoxic T-lymphocytes (CTLs) against HIV. Antibodies, according to the Merck researcher, "are unlikely to be sufficient for protection." He noted that: 1) neutralizing antibodies generated by current candidate HIV vaccines "are of exceptionally low potency" and are likely to be limited by the envelope's glycosylation; 2) antibodies generated by HIV immune globulin have failed to protect neonates from HIV; and 3) monoclonal antibodies have shown a limited ability to neutralize primary isolates of HIV.

In contrast, HIV-specific CTL responses, according to Emini, appear to dramatically reduce HIV levels in acute infection and correlate with a low viral load in HIV-infected individuals.

Merck's HIV DNA program will initially focus on a *gag/pol* construct. "But," he cautioned, "DNA alone may not be sufficient. We may need to include another vaccine. And because the immune responses to HIV are complex, we will only move into human trials when warranted."

### The case for antibodies

Susan Zolla-Pazner of New York University Medical Center reviewed the potential role of antibodies in protecting against HIV. She noted that in many viral diseases CTL responses can control infection, but antibodies prevent infection from taking hold ("sterilizing immunity").

Zolla-Pazner described a number of studies demonstrating that sera from HIV-infected individuals could neutralize some primary isolates of HIV. "The pendulum," she said, "has begun to swing in the direction that antibodies can neutralize primary isolates. However, at this point we don't have a clue as to what distinguishes viruses from being easy or difficult to neutralize."

In designing a vaccine, Zolla-Pazner proposed using vaccines constructed from multiple strains of HIV. "Polyvalent vaccines have protected against pathogens characterized by antigenic variability. The vaccine for streptococcal pneumoniae," she

noted, "is constructed from 23 different strains of pneumococcus."

### PMC to use VaxGen gp120 boost

In a press conference, Michel Klein of Pasteur Mérieux Connaught (PMC) announced that the company will use VaxGen's bivalent gp120 (AIDSVAX®) in a trial comparing different canarypox vectors, as part of a "prime boost" combination. The Phase I study, to be conducted in the U.S., will compare the canarypox vectors: vCP205, vCP1433 and vCP1452. All participants will also be given with AIDSVAX as a boost. The trial will enroll 100 people; 50 participants have already been enrolled.

Why isn't PMC using Chiron's gp120 as it had in previous prime boost studies? The reason, according to Klein, is that the VaxGen product is derived from a primary isolate. The decision increases the likelihood that PMC will use AIDSVAX in a Phase III prime boost study.

Klein also reported that a Phase I study in France will examine vCP1452 in combination with a lipopeptide cocktail. Other approaches to be studied include: a vCP1452 vector (derived from a clade E primary isolate) combined with a clade E envelope boost in Thailand; a VLP (virus-like particle containing *env*) vaccine derived from primary isolates; and clade A and E canarypox vectors in Uganda and the Ivory Coast.

### Review of data on PMC's canarypox vectors

Larwence Corey of the University of Washington presented data from clinical trials of PMC's canarypox vectors. In two studies of vCP205 that enrolled a total of 220 people, approximately 30-40% of vaccinees had detectable CTLs at each point of measurement and 65-75% had CTLs at least at one point. Corey noted that after four doses, the number of vaccinees with newly detectable CTLs levels off. Positive CTL responses in placebo recipients were less than 8%.

The CTLs, as measured by the laboratory assay, are broader and more durable than had been expected. Early data suggests that approximately half of vaccinees had measurable CTLs against HIV *gag* and *env* one year after the last immunization.

Immunizing with the canarypox vectors and then later with a gp120 boost (sequential immunization) appears to generate slightly higher CTLs than administering both vaccines at the same time (simultaneous immunization). In the sequential arm, approximately 68% had measurable CTLs, compared to 60% in the simultaneous arm. (The Phase II prime boost study now underway in the U.S. uses simultaneous immunization of canarypox and gp120.)

Does simultaneously immunizing with the antibody-inducing

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*A key question: why do 30% of those vaccinated with the HIV canarypox vectors show no CTLs against HIV?*

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gp120 and the CTL-inducing canarypox vectors shift the immune response away from CTLs? (A “Th1-Th2” switch has been proposed by a number of researchers.) “We have talked about this but we don’t have enough data to know,” says Kent Weinhold of Duke University, who also presented data on the canarypox vectors.

According to Weinhold, the ability of canary pox vectors to induce immune responses to the core protein, *gag*, may be critically important. Early canarypox constructs expressing gp160 (vCP125) showed very limited cross clade reactivity, but once *gag* was added (vCP205), much greater breadth of CTL response was seen. This is not surprising since *gag* is more highly conserved than the envelope.

Are these ALVAC-induced CTL responses real? In tests of CTLs induced by vCP300, 14 of 18 samples were able to kill cells infected with primary isolates of HIV. But both Corey and Weinhold noted that the real value of these CTLs can only be evaluated in controlled clinical trials.

Another key question: Why do 30% of vaccinees seem to have no evidence of CTL response to HIV? These individuals do generate CTLs to other viruses. “At this point,” says Weinhold, “we just don’t know if it is the limits of the assay or the vaccine.”

### Marc Girard on HIV vaccines

Marc Girard of the Institut Pasteur (and a member of IAVI’s Scientific Advisory Committee) provided a broad overview of AIDS vaccine research in animals. Like Emilio Emini, he noted that antibodies may not be required for protection, particularly against mucosal challenge.

The French researcher called for new candidate vaccines to be based on primary isolates and for animal challenges to be conducted via the mucosal route to best mimic the predominant mode of HIV transmission. Girard ended his talk by noting that “we still know almost nothing of the immune correlates of protection.”

### Debate on live attenuated vaccines

Charles Farthing, a Los Angeles physician who has proposed human tests of live-attenuated HIV vaccines, and Ruth Ruprecht, a researcher at the Dana-Farber Cancer Institute who first reported that attenuated SIV could cause disease in newborn monkeys, engaged in a lively debate about live HIV vaccines.

According to Ruprecht, live SIV vaccines (attenuated by removing three SIV genes, including *nef*) have caused simian AIDS or death in all nine newborn monkeys given the vaccine. In addition, 4 of 15 adult macaques show signs of AIDS. Ruprecht also noted that at least four other labs have reported adult monkeys immunized with *nef*-deleted SIV that have developed AIDS.

Farthing suggested that *nef*-deleted SIV has provided the

most effective protection of any vaccines so far tested in monkeys. He also noted that the vaccine he proposes for human trials would be safer because it contains additional genetic deletions than the vaccine tested by Ruprecht. Farthing also pointed to an Australian cohort of blood transfusion recipients infected with a *nef*-deleted strain of HIV that has remained healthy for over 15 years.

However in the question period, Jenifer Learmont of the Sydney Red Cross reported that some in the Australian cohort now show a CD4 decline. The information was discussed at a meeting on live attenuated vaccines held at the U.S. National Institutes of Health (NIH) in May. However, Ruprecht, bound by the guidelines of the meeting, could not to report the data.

Farthing, for his part, continues to maintain that “the only way to find out if live attenuated vaccines work is to test them in humans. SIV is not HIV and monkeys are not humans.” But as one writer remarked, while leaving the session, “Farthing can’t have it both ways, on one hand pointing to the protection in monkeys as being persuasive, but then suggesting that the safety data is irrelevant, because monkeys are not humans.”

### Vaccinia construct protects some monkeys

Genoveffa Franchini of the U.S. National Cancer Institute (NCI) presented more data about a vaccinia vector (NYVAC) that protected some monkeys against mucosal challenge with pathogenic SIV (see *IAVI Report*, vol.3, no.2). The monkeys were immunized with NYVAC (expressing key SIV genes and the cytokines IL-2 and IL-12). A total of four immunizations were given over 12 weeks. Half of the animals were challenged intravenously with pathogenic SIVmac251, the other half by intrarectal mucosal exposure. Macaques exposed to SIVmac251 usually die within 2 years, half of them within 6 months.

Of the monkeys challenged mucosally, 5 of 11 had a transient peak of SIV and then appeared to clear the virus. In

contrast, all 12 of those challenged intravenously became infected. But even in this group, there was some evidence of slower progression. Protection did not seem to correlate with higher levels of CTLs, neutralizing antibodies and chemokine production. The IL-12 and IL-2 arms developed higher CTL responses, but no greater protection was seen.

Franchini told the *IAVI Report* that NCI researchers will soon begin a new study, immunizing monkeys with SIV DNA and a NYVAC boost. “We will use intramuscular, intranasal and intrarectal immunizations. Our goal is to increase the 50% protection we saw against mucosal challenge in our last study to 80% in this upcoming study.” (Abstract 21200)

### Neal Nathanson talks about vaccine research

In a press conference, Neal Nathanson, the newly appointed

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*Surprisingly, monkeys protected by the NYVAC/vaccinia vector do not seem to have higher levels of CTLs, antibodies or chemokines.*

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## One Trial, Many Opinions

VaxGen's Phase III gp120 trial continues to make news. Recently, the NIH announced that it would provide some resources to support ancillary research in conjunction with the AIDS VAX® trial. During the World AIDS Conference and the weeks preceding it, well known authorities presented starkly different opinions about the trial and the product being studied.

**"Indications are that AIDS VAX is safe and will likely protect humans from HIV-1 infection."**

-Abstract 33223, submitted by D. Francis et al.

**"No scientist that I know in the vaccine field has any expectation at all that the vaccine is going to be effective, and I can list ten or 15 names at the drop of a hat."**

- Ronald Desrosiers, New England Regional Primate Center  
(in the conference's official daily newspaper)

**"The vaccine is interesting because it contains a primary isolate. While it is unlikely to be sufficient because it does not generate a CTL response, there are some good reasons to do this trial."**

-Marc Girard, Institut Pasteur  
27 June 1998

**"Speculation by scientists, in reaction to the first crystallography pictures of the HIV envelope protein gp120, that an AIDS vaccine based on gp120 proteins is unlikely to work is premature and incorrect. To the contrary, the data ... validate the scientific basis on which VaxGen has developed its AIDS VAX vaccine."**

-Phillip W. Berman, VaxGen (press release, 18 June 1998)

**"One doesn't need the crystal structure to put a nail in that coffin."**

-Joseph Sodroski, Dana-Farber Cancer Institute  
Speaking about prospects for current gp120 vaccines  
(*The New York Times*, 18 June 1998)

**"The Phase III gp120 trials are quite reasonable. If we don't begin now, we will never know if it will be effective."**

-Hans Wigzell, Karolinska Institute  
26 June 1998

**"Although many researchers are pessimistic about the chance of this vaccine demonstrating protection, this trial should nevertheless be seen as a positive move."**

- Editorial, *Nature Medicine*  
August 1998

**"There are important things we can learn from this trial including insights about how to conduct a Phase III trial, the ethical issues involved, and, hopefully, whether the product is effective."**

-Neal Nathanson, newly appointed director of the NIH Office of AIDS Research

**"This trial is a watershed. But we will clearly need many more efficacy studies throughout the world."**

-Seth Berkley, IAVI (*The New York Times*, 4 June 1998)

director of the NIH Office of AIDS Research (OAR), predicted that NIH funding for HIV vaccine research would continue to increase at 15% above inflation. "However," he added, "vision and leadership are as important as funding."

The new OAR head expressed support for VaxGen's Phase III trial, saying that he is "not interested in getting into squabbles. We will welcome any ideas." Nathanson said he will try to refocus some of NIH's vaccine efforts towards "goal directed research."

Nathanson also said that NIH Director Harold Varmus "has been working very hard to recruit top candidates for the director of the NIH Vaccine Center. He has taken flack, but he wants to pick the best person. I think that is absolutely the proper approach to take," he added.

### HIV DNA plus fowlpox prime boost

Stephen Kent of the Macfarlane Burnet Centre in Australia reported data on a DNA/poxvirus "prime boost" combination given to macaques. The monkeys were immunized with HIV DNA (*env/gag*) and an avipox vector (encoding *env* and *gag/pol*). The HIV DNA was administered by gene gun. HIV-specific CTL responses generated by the DNA increased significantly (up to 20-fold) with the fowlpox boost. Upon challenge with a non-pathogenic, homologous HIV, all four of the immunized macaques were protected. Kent noted that CTL levels approached those seen in acute infection.

The Australian researcher speculated that boosting with a CTL-inducing construct (such as a poxvirus) may be preferable to using an antibody-inducing envelope protein. "An envelope protein may divert immune response to an antibody response," he suggested.

The DNA construct was supplied by Harriet Robinson of Emory University. David Boyle, another Australian researcher, developed the poxvirus vaccine. (Abstract 21198)

### Higher levels of chemokines in protected monkeys

Researchers from the Swedish Institute for Infectious Diseases in Stockholm and Guys Hospital in London reported that higher levels of beta chemokines may be associated with protection against AIDS in monkeys. The researchers vaccinated cynologus macaques with live attenuated SIV or SHIV (six with an attenuated clone of SIV, four with SHIV-4).

Upon SIV challenge, 3 of 6 in the SIVmac group and 1 of 4 in the SHIV group were completely protected, while all control monkeys became infected. The protected animals had, on average, higher levels of the beta chemokines RANTES and mip-1 alpha on the day of challenge compared to the control group. Interestingly, these animals even had higher levels of beta chemokines before vaccination. In addition, blood samples from protected animals could more effectively suppress virus. The researchers concluded that beta chemokines play a role in

protection against SIV and SHIV. (Abstract 11239)

### **Therion's vaccinia TBC-IIIB plus gp120**

Michael Keefer of the University of Rochester presented data on TCB-IIIB, a vaccinia vector expressing *env/gag*. In a Phase I study, TCB was administered by scarification, intradermal infection or subcutaneous injection. Only vaccinia-naive individuals were included. A second immunization of TCB was given (either at the same dose or one 100-times higher). Researchers found that the vaccinia vector was well-tolerated, even at the high dose boost.

When TCB was given with a gp120 boost, all routes of administration of vaccinia were associated with "clinical takes", i.e., participants with skin breakdown. Antibody responses were seen in those immunized intradermally and subcutaneously, but not in those immunized by scarification. Data on the CTL response has not yet been analyzed or presented. (Abstract 21199)

### **Comparing live attenuated SIV**

Mark Lewis of the Walter Reed Army Institute of Research (WRAIR) presented data on a study comparing live attenuated vaccines derived from two different *nef*-deleted strains of SIV – SIVmac239 (rhesus macaques) and SIVPbj6 (pigtail macaques).

A total of 40 monkeys were immunized. By week 20, approximately 50% of those vaccinated with the SIVmac239 strain and 90% immunized with SIVPbj6 had controlled the vaccine virus. Moreover, *nef*-deleted SIVmac239 failed to prevent infection upon challenge with other SIV (E660) or SHIV (89.6P) strains, while SIVmacPbj6 protected 50% of monkeys challenged with these other strains. The researchers concluded that *nef*-deleted macPbj strain of SIV is safer and protects better than SIVmac239. (Abstract 11238)

### **More on antibodies**

Abraham Pinter of the Public Health Research Institute in New York City reported that rats and monkeys immunized with the VI/2 domain of the HIV envelope (expressed as a protein) produced antibodies that neutralized a number of different HIV clades. Sera from the immunized animals neutralized HIV primary isolates from clades A, B, C, D and E. According to Pinter, these findings suggest that some subunit vaccines may be able to induce antibodies that protect against a wide range of HIV strains. (Abstract 21194)

### **Adenovirus vector with peptide boost**

NCI researchers presented initial data on the combination of an adenovirus vector and a polymeric peptide (peptomer) vaccine in rhesus monkeys. Six monkeys were immunized with an adenovirus vector expressing *env*. Three of these were boosted with the peptomer, which was derived from the CD4 binding site of the viral envelope; the other three were boosted with gp120.

Two of three monkeys in each arm showed significant CTL response. The gp120 boost elicited strong neutralizing antibodies while the peptomer boost generated strong T-cell proliferative responses. NCI researchers plan to evaluate the adenovirus/peptide combination against an intrarectal challenge with a pathogenic SIV strain. (Abstract 11241)

### **Intranasal administration of HIV DNA vaccines**

Researchers led by Kenji Okuda of Yokohama City University reported that intranasal immunization of HIV DNA vaccines distributed the DNA more widely in the tissue of mice than intramuscular immunization. In addition, intranasal administration induced a strong IgA response in lymph tissues, which may be more significant in light of the report that HIV-resistant Kenyan sex workers have higher levels of HIV IgA in genital secretions. The researchers also reported that administering HIV DNA with different adjuvants could enhance either humoral or cell-mediated immunity. (Abstracts 21203, 21205)

In another study, Okuda compared three different types of *env* in a DNA plasmid (a clade B lab strain, a clade B primary isolate and a clade E unknown tropism) in mice. He reported that the plasmid encoding the primary isolate induced the highest CTLs. (Abstract 21211)

### **Cross-clade immune responses**

Researchers from the WRAIR and the Thailand's Armed Forces Research Institute reported that significant numbers of North Americans infected with clade B HIV and Thais infected with clade E may be able to generate cross-clade CTLs. The CTL responses were specific for all four HIV proteins tested (*gag*, *pol*, *env* and *nef*), but most frequently to *gag*. The researchers conclude that *gag* is likely to be an important antigen in a

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## **IAVI at Geneva**

IAVI released its *Scientific Blueprint for AIDS Vaccine Development* on the first day of the International Conference. The Blueprint, which outlines a clear path to put HIV vaccine development on a fast track, generated significant excitement and media coverage at the meeting. IAVI also organized a series of separate forums with NGO representatives and leaders of women's organizations. Meetings were also held with developing country, scientific and gay/lesbian journalists to gather support for AIDS vaccine development. At the conference itself, IAVI President Seth Berkley co-moderated a bridging session, "Overcoming Obstacles to Human Trials of AIDS Vaccines." The Blueprint is available at IAVI's website at [www.iavi.org](http://www.iavi.org).

# HIV “Resistant” Individuals May Point Way to a Vaccine

Rupert Kaul of the University of Nairobi presented detailed immunologic data on Kenyan sex workers who appear to be resistant to HIV. The resistant sex workers, according to Kaul, have strong evidence of HIV-specific IgA antibody in their genital secretions.

In total, 76% (or 16 of 21) of the resistant sex workers showed evidence of HIV IgA, while only 26% of HIV-infected sex workers and 11% of low risk women had such a response. Moreover, in the low-risk group, the presence of HIV-IgA in the genital secretions correlated with a relatively higher risk.

Surprisingly, researchers did not find that HIV-IgA was more prevalent in the saliva of the resistant sex workers. They are now looking at HIV IgA levels in the blood of these sex workers. In addition, another antibody response, HIV-specific IgG, was less prevalent in the resistant sex workers and more common in those infected with HIV.

Kaul also reported that 55% (or 11 of 20) of the resistant sex workers, but only 22% of the HIV-infected sex workers, showed evidence of an HIV-specific T-helper response. Notably, these cellular responses did not correlate with the presence of HIV IgA in genital secretions.

When asked whether active STDs could be inducing IgA in the genital secretions, Kaul noted that only one case of an STD (gonorrhea) was found in the resistant sex workers. Are there ways to induce an HIV-specific IgA response in the mucosal system? According to Kaul, HIV is not particularly efficient at inducing mucosal IgA, but some immunogens, including cholera toxins, appear to induce mucosal IgA without IgG. (Abstract 31101)

## More data on “exposed but uninfected” individuals

There was a significant amount of other reports on HIV-resistant or “exposed but uninfected” individuals.

Thai researchers, comparing exposed but uninfected sex workers with HIV-infected sex workers, found that five of the eight “resistant” sex workers had evidence of HIV-specific CTLs. (Abstract 31120) The same researchers also reported that cultures taken from the resistant sex workers in Thailand can more easily suppress HIV than cultures taken from HIV-negative controls. The suppressive activity was similar to that seen in cultures taken from HIV-infected sex workers. (Abstract 31140)

Researchers from the Swedish Institute of Infectious Diseases reported that HIV-2 “exposed but uninfected” individuals in sero-discordant relationships have increased levels of the beta chemokines RANTES and mip1-alpha compared to HIV-2-infected individuals and low-risk uninfected individuals. (Abstract 31133)

According to researchers at the University of California at San Francisco, at least half of 60 “exposed but uninfected” individuals had a strong CD8+ response to HIV as evidenced by the ability of their CD8+ cells to inhibit HIV. This CD8 response did not appear to correlate with HIV-specific CTL responses. (Abstract 31143)

A significant number of HIV-negative Ethiopian immigrants now living in Israel have evidence of prior exposure to HIV. Of 100 individuals studied

by Israeli researchers, 42 showed signs of HIV-specific T-cell proliferation. In addition, 9 of 45 individuals studied had evidence of HIV-specific IgA in the serum. (Abstract 31144)

French researchers reported that in eight high-risk, HIV-exposed but uninfected individuals in sero-discordant relationships, HIV-specific CTL activity was found in two (25%) of these individuals. (Abstract 31146)

“Exposed but uninfected” sex workers in Abidjan have higher levels of beta-2 microglobulin compared to low risk sex workers, according to researchers from the Ivory Coast, Belgium and the U.S. (Abstract 31147)

Australian researchers reported that HIV-negative infants born to infected mothers had significantly higher levels of HIV-specific CTL responses. These responses, according to the researchers, could be detected as early as one day after birth and were still present 20 months after birth. (Abstract 31157) ♦

## UNAIDS Ethics Meeting

By Julian Meldrum

UNAIDS held a pre-conference workshop on the ethics of vaccine trials. The workshop reached a consensus on a number of issues including the need for individual informed consent by trial participants and that current ethical guidelines should be changed to allow a vaccine to be tested in a developing country before being tested in the sponsoring country (which would most likely be in North America or Europe).

There was disagreement over the medical care to be provided to trial participants who become infected with HIV. Brazilian and some U.S. participants argued for U.S.-style access to antiretrovirals, even if they were not generally provided in the country where the trial was being conducted. Thai, Ugandan and other international participants said such standards would create unreasonable incentives to participate in trials, undermining their voluntary

basis. The incentives, it was suggested, would not be sustainable after the trial. In addition, they could create significant financial and logistical obstacles in many countries that would slow down essential vaccine development. To date, most HIV vaccine trials have been conducted in North America or Western Europe.

As a true consensus could not be reached, a “procedural” consensus was agreed upon: each country could determine the level of treatment to be provided to trial participants, but that standard could not be less than the best local attainable standard of care.

The workshop participants agreed that local consultation issues should be undertaken, and that decisions must ultimately rest with the country/community in which the trial is being held.

*Julian Meldrum is Editor of the Body Positive Newsletter, London, England*

# Taking a Closer Look at Trial Participants

At this year's international conference, a number of researchers reported data about the individuals who participate in HIV vaccine trials and cohort studies. Key issues that were examined included: why people volunteer for HIV vaccine trials, concerns raised by trial participants and risk behaviors reported by such individuals.

### **Deciding whether to participate**

In looking to determine why individuals participate in AIDS vaccine trials, Brazilian researchers surveyed a cohort of 662 gay and bisexual men. The most frequently cited reasons by participants were a desire to collaborate with science (20%), solidarity (22%) and perceived personal benefit (22%). The most frequently cited reasons for not participating: fear of side effects (38%) and lack of credibility of the product. Responses did not vary according to education level. (Abstract 14148)

In a study examining the willingness of injection drug users (IDUs) in Thailand to participate in an HIV vaccine study, researchers provided 193 IDUs with informational counseling sessions. A majority of participants — 51% at baseline and 54% at follow-up — expressed a willingness to participate in a vaccine trial.

Altruism was the most frequently cited reason for participating (79%), while the possibility that a vaccine might cause harm was the most commonly cited barrier (31%). (Abstract 43548)

Ugandan researchers studied attitudes about AIDS vaccine trials in a cohort of soldiers (ages 23-36). After 12 months, the number of soldiers believing that vaccines cause AIDS decreased from 27% to 1%. A large majority — 88% at entry, 83% at 12 months — said they were willing to participate in a vaccine trial. At 24 months follow-up, 3.8% of the participants had become infected with HIV. However, the number of new STDs decreased from 38% to 1% over the same period. (Abstract 14254)

In another study of young men in the Ugandan military, 44% of those willing to participate in an HIV vaccine trial said they would tell their wife or girlfriend about their participation. However, 18% said they would tell no one including their doctor, family and friends. A large number (45%) felt that people would assume they had AIDS if they participated in a trial. Nevertheless, 79% said that they would still be willing to participate. (Abstract 14278)

In attempting to identify opinions about participating in AIDS vaccine trials, U.S. researchers conducted in-depth interviews with 91 individuals at high-risk for HIV infection (including gay and bisexual men in San Francisco, injection drug users in Philadelphia and African-Americans in Durham.) The most commonly stated concern about enrolling in a trial was for scientists to be completely open about all aspects including: 1) expected rates of success; 2) how the

candidate vaccine compares with others; and 3) expected side effects. (Abstract 43547)

In a much larger study, researchers followed 865 uninfected women at high-risk for HIV in five U.S. cities. Of the participants, 41% were recent injection drug users and 20% had a recent sexually transmitted disease. At 24 months, only 70% of enrollees were still available for follow-up. Women over 35 and those with a history of injection drug use were more likely to follow-up. Race, educational level, employment and giving altruistic reasons for enrolling were all not related to follow-up. (Abstract 23447)

### **New infections/risk behaviors**

Thai researchers reported that in cohort studies of 480 women followed in community clinics, rates of new HIV infections were approximately 2% per year over 24 months, despite intensive counseling, free condoms and STD treatment. Retention of participants was 94% after 18 months. Approximately 25% of those enrolled expressed an interest in participating in a vaccine trial. The major advantage cited was obtaining health benefits. Major barriers were: fear of side effects, discrimination and sex partner disapproval. (Abstract 33212)

According to a cohort of 386 gay/bisexual men and 621 IDUs in Canada, rates of new HIV infections in these populations total about 2% per year. In a survey of the participants, 63% of the gay/bisexual men and 83% of IDUs expressed a willingness to enroll in an AIDS vaccine trial. A high perceived threat of HIV infection was related to a willingness to participate. Among the IDUs, participation in needle exchange programs

closely correlated with a willingness to participate in trials. (Abstract 33214)

Brazilian researchers reported that in recruiting gay and bisexual men for cohort studies, the number of potential participants who were HIV-infected at entry was 7.6% in Belo Horizonte, 12.5% in Sao Paulo and 24% in Rio de Janeiro. (Abstract 33217) The researchers also reported that, among bisexual

men in the Belo Horizonte cohort, there was a reduction in the incidence of unprotected anal sex, but an increase in unprotected vaginal sex. (Abstract 23448)

U.S. researchers reported that of 3,257 men having sex with men (MSM), 770 male IDUs, 354 female IDUs and 511 high risk women having sex with men (WSM) enrolled in HIVNET studies in 8 U.S. cities, approximately 1.36% per year became infected with HIV. The highest rates of new infections were seen among MSM (1.54%), female IDUs (1.26%) and WSM (1.15%). (Abstract 43543)

### **Access to vaccines**

Providing access to safe, effective, already approved vaccines appears to be a problem, even in the most wealthy countries. A study by University of California at San Francisco researchers reported that despite the development of a safe and effective hepatitis B vaccine years ago, many of those at high risk do not have access to the vaccine. Of 428 gay and bisexual San Francisco men (ages 18-29), 22% had already been exposed to hepatitis B (HBV) and of these, 5% had chronic HBV infection. Yet despite the obvious risks, only 27% in the cohort had been vaccinated for HBV. (Abstract 43233) ♦

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*The most common concern among participants: that scientists be completely open about all aspects of the trial and the vaccine being tested.*

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# Key Vaccine Reports at Human Virology Meeting

The Institute for Human Virology (IHV), a U.S.-based research institute led by Robert Gallo and located at the University of Maryland, held its annual meeting on 23-28 August 1998 in Baltimore. The meeting featured a significant number of presentations on AIDS vaccine research. Some of the highlights are discussed below.

## VEE replicons show promise

Robert Johnston of the University of North Carolina presented data showing that a Venezuelan Equine Encephalitis (VEE) replicon vaccine appears to protect some monkeys against intravenous challenge with pathogenic SIV.

The non-replicating vector consists of the alphavirus VEE, with key genes deleted and replaced by parts of SIV *gag* and gp160. Because it lacks several genes essential to forming

VEE particles, the replicon can infect but does not produce progeny virus. Johnston described it as "a single shot virus that doesn't spread." The advantages of the VEE replicon are that: 1) it provides high levels of expression of the antigen; 2) it targets lymphoid tissues; and 3) it induces mucosal and systemic immunity. (See *IAVI Report* vol.3, no.2.)

A total of four monkeys were immunized with VEE-SIV; two subcutaneously and two intravenously. Another four monkeys were given a control vaccine. After four immunizations, three of four immunized animals had SIV-specific CTLs and one of four had neutralizing antibodies. On day 360, the monkeys were boosted with VEE expressing gp140. Three of four then developed neutralizing antibodies.

The monkeys were then challenged intravenously with E660, a highly pathogenic SIV strain. Two control animals developed immune suppression and high viremia and were euthanized at 11 weeks. The other two controls have "climbing" viral loads. But of the vaccinated monkeys, two of four have undetectable virus levels. Of the two others,

one has "a steady" viral load, the other (which had no SIV-CTLs) has a viral load similar to the control animals. Overall, the average "peak" virus load in the vaccinated monkeys was two orders of magnitude lower than the control monkeys.

Johnston described the results as "very encouraging" and said the group may add the rest of *gag* and other SIV genes to the VEE vector and, perhaps, use a protein boost. He also noted that the VEE replicon has been shown to be safe in over 1000 rodents and 40 macaques. At a presentation one week later at the NIH's AIDS Vaccine Committee, Johnston said that development

could be slowed because "we are resource limited."

The same VEE construct has shown extremely promising results in protecting monkeys against the extremely lethal Marburg virus, which

is related to Ebola virus.

## Bacterial vectors for HIV

David Hone of IHV discussed data on salmonella and other bacterial vectors as HIV vaccines. The advantages of salmonella vectors, according to Hone, are: 1) they are very inexpensive to produce; 2) they are simple to administer (orally); and 3) they can induce mucosal and systemic immunity.

A salmonella vaccine expressing gp120 developed by Hone and George Lewis (also of the IHV) is now in a Phase I trial at Johns Hopkins University. (Hone publicly thanked the late Mary Lou Clements-Mann and Pat Fast, formerly of NIAID, for their help in getting the trial started.) To date, two doses have been tested and the vaccine appears to be safe and well tolerated.

Hone and Lewis are also designing bacterial vectors which can deliver DNA vaccines. They have developed a salmonella vector that carries an HIV DNA vaccine (expressing *env*). Studies in mice show that the construct generates measurable CTL responses. The IHV researchers are also developing a salmonella vector expressing

HIV *gag* and are considering testing the salmonella vaccine with a gp120 boost.

## "Fusion competent" vaccines

Jack Nunberg of the University of Montana presented data on a novel "fusion-competent" vaccine that appears to generate potent neutralizing antibodies in mice. The vaccines are unique in that they present a functioning envelope protein in conjunction with CD4 and a co-receptor.

According to Nunberg, the short-lived interactions and conformational changes that occur when the envelope fuses with CD4 and a co-receptor may expose critical targets for generating neutralizing antibodies. By using a "functioning" envelope, he suggests that more powerful antibodies can be elicited.

When Nunberg's team looked at fusion incompetent vaccines (which presented a non-functioning envelope protein), the antibodies generated in mice failed to neutralize diverse primary isolates of HIV. But sera from mice immunized with the fusion competent vaccines neutralized primary isolates from a number of HIV and SHIV strains.

Duke University's Dani Bolognesi called Nunberg's approach "very interesting." But he cautioned, "we need to see what happens when it is tested in monkeys." Nunberg is currently attempting to get funding for such studies. His research so far has been supported by a grant from the American Foundation for AIDS Research.

## DNA plus MVA

Andrew McMichael of Oxford University discussed mechanisms by which HIV may evade early CTL responses to the virus. McMichael also briefly discussed animal studies of a DNA and modified vaccinia Ankara (MVA) prime boost combination developed by his lab. The combination is being studied for both HIV and malaria. Early studies in macaques, according to McMichael, suggest that the SIV DNA generates CTLs which increase substantially with the MVA boost. The CTL levels are now in the range of what is seen in macaques chronically infected with HIV. ♦

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*In one very encouraging study, a VEE replicon vaccine has protected some monkeys against an intravenous challenge with pathogenic SIV.*

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# NIH AIDS Vaccine Panel Meets, Discusses Program Changes, Vector Research

The U.S. NIH's AIDS Vaccine Research Committee (AVRC) met on 2-3 September 1998 in Bethesda. The committee, which is headed by California Institute of Technology President David Baltimore, heard reports about changes in the NIH vaccine program, new programmatic efforts and reports from a number of researchers (including Bob Johnston and David Hone, who also presented at the IHV meeting one week earlier). Highlights of the AVRC meeting are discussed below.

## NIAID Vaccine Program

Jack Killen presented information on changes in the HIV vaccine program at the National Institute of Allergy and Infectious Diseases (NIAID). Killen began by noting that Peggy Johnston would be leaving IAVI to lead NIAID's HIV vaccine program (see Vaccine Briefs, page 12). He then discussed changes in NIAID's two vaccine trial networks: the AIDS Vaccine Evaluation Group (AVEG) and HIVNET. These two networks are being combined into one vaccine trials group (VTG) that will coordinate all NIAID HIV vaccine trials in the U.S. and internationally. At present AVEG is responsible for Phase I and II trials and HIVNET for prevention, Phase III vaccine trials and some Phase II studies. A separate HIV prevention trial network is also planned. In response to questions, Killen said that the prevention network still may be used for Phase III studies and admitted that "there could be a substantial overlap in investigators."

Killen also outlined broad plans for "HIV vaccine design and development teams" which would attempt to advance promising vaccine concepts to product development. These teams, according to Killen, could be part of fiscal year 2000 budget.

## Comparing promising approaches in monkeys

Norman Letvin presented plans for comparative monkey studies of a number of different AIDS vaccine approaches. According to Letvin, a researcher at Harvard and member of the AVRC (and IAVI's Scientific Advisory Committee), the non-human primate model is now "mature enough" to allow comparisons between candidate HIV vaccines.

A group chaired by Letvin and NIAID's Alan Schultz looked at how to initiate standardized, comparative monkey studies in terms of strains of SIV, species of monkeys and route of challenge. They proposed a set of experiments which will compare different approaches including: modified vaccinia Ankara (MVA), vaccinia, canarypox, DNA and perhaps NYVAC. Comparative antigens, promoters, and boost strategies will be used. Three immunizations will be given and the challenge will be with a pathogenic SHIV 89.6P strain which will be administered mucosally.

The studies will measure disease progression via viral load and survival. To standardize the comparison, trial organizers will have to reconstruct all the vectors. Letvin announced that one leading company has already agreed to allow its construct to be included in the comparative study. A gp120 boost will be used if VaxGen agrees to provide its product. "It wasn't easy to reach agreement on the overall standards to be used," said Letvin. "We hope this project establishes momentum in the field and allow us to test and compare all promising AIDS vaccine concepts."

## The role of T-helper responses

Bruce Walker of Massachusetts General Hospital discussed findings by his lab about the role of T-helper cells in controlling HIV infection and the implications they may have for HIV vaccine development. According to Walker, p24 specific T-helper cells appear to correlate with long term non-progression. Moreover, individuals treated with potent anti-retroviral therapy right after exposure appear to maintain these responses. These individuals also have strong *gag*-specific CTLs.

Antibodies, Walker believes, may not be a critical immune response in these cases. "In treating right after exposure, we see that antibodies do not increase until T-helper responses are well established."

Walker also discussed his lab's work in quantifying levels of HIV-specific CTL responses in patients. He suggested that the ELISPOT method currently used by his research team would be a very useful method of measuring CTLs generated by candidate HIV vaccines.

## NIAID MVA Studies

Bernard Moss of NIAID presented data about the use of MVA as an AIDS vaccine vector. MVA is a vaccinia virus that has been attenuated by more than 570 passages in chicken embryos. It can handle a large capacity of genetic material, which allows for high levels of expression.

According to Moss, MVA has a strong safety profile. It has been used as a smallpox vaccine without significant side effects in humans. It does not replicate in human and most other mammalian cells and, unlike vaccinia, appears to be non-pathogenic in immune-suppressed animals.

Moss, working with fellow NIAID researcher Vanessa Hirsch, has conducted a series of studies of MVA vaccines in monkeys. In an early study, an SIV MVA vaccine given with a whole-killed SIV boost, provided long term protection against pathogenic SIV in two of four monkeys. In another study, measurable SIV-specific CTL responses were seen in macaques after only one immunization of an MVA construct.

The most recent study compares: 1) MVA expressing SIV *env*; 2) MVA expressing SIV *gag/pol*; 3) MVA expressing SIV *env, gag, pol*; and 4) a control vaccine. A total of 24 monkeys will be immunized; six of these will be control animals given MVA with no SIV antigens.

One concern was that passaging the MVA in chicken embryos may expose vaccinees to endogenous retroviruses from the chicken cells. However, M. Carolyn Hardegree of the U.S. Food and Drug Administration responded that many currently-licensed products are grown in chicken embryos and, to date, no evidence has been found of infectivity with endogenous retroviruses. "We don't see this issue as a big hurdle at this time," she added.

## Other Issues

Towards the end of meeting, David Baltimore raised the possibility of whether, in order to move things forward, "NIH is going to have to make bigger bets on some promising approaches that currently lack industrial support." The AVRC, he suggested, might consider helping to identify a number of promising concepts and "putting real muscle behind them."

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*The NIH may have to make "bigger bets" on promising vaccine approaches that currently lack industry support.*

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# A Forceful Champion of Vaccines

by Pat Fast, M.D., Ph.D. and Bill Snow

As longtime leaders in the fight against AIDS, Jonathan Mann and Mary Lou Clements-Mann were tenacious and outspoken in working to end the global epidemic.

In the field of HIV vaccine research Mary Lou, in particular, played a special role. As the principal investigator of the Johns Hopkins University HIV vaccine clinical trials site, she had a deep commitment and vision about the role of vaccines in improving global health. She clearly understood that only a safe and effective vaccine could end the HIV epidemic. As a clinical investigator, Mary Lou possessed a meticulous attention to detail and was ever mindful of the well-being of volunteers who participated in vaccine trials. She did her utmost to further research in the U.S., and worked to advance the capacity of developing countries to plan and conduct vaccine trials.

In the early 1990s, when HIV vaccine trials were first contemplated in Africa, Asia and Latin America, Mary Lou and her colleagues organized a workshop at Johns Hopkins that brought together leaders from a number of countries to review principles of vaccine research and consider designs for efficacy trials. With the coordinators of the WHO Global Program on AIDS (now UNAIDS), she traveled to several countries to meet with national authorities and scientists. Her guidance and practical assistance in developing the National Vaccine Development Plans for Thailand and Uganda were critically important. She continued to work with researchers from these countries to facilitate dialogue, learning, and independent decision-making about HIV vaccine research.

Within the U.S. NIH-sponsored AIDS Vaccine Evaluation Group (AVEG), Mary Lou was the principal investigator for the first trial of Genentech's gp120 (the precursor of the VaxGen vaccine now in Phase III trials) and the first trial of a canarypox vector from Pasteur Mérieux Connaught (the precursor of the "prime" in the prime-boost Phase II trial underway). She was also the only AVEG investigator to accomplish a truly unique scientific task –

taking a novel product developed in an academic center into a proof-of-concept Phase I trial without corporate sponsorship (a Salmonella-gp160 oral vaccine developed at the University of Maryland). This achievement required close working relationships with scientists across several research institutions and an enormous amount of hard work and patience.

Mary Lou was an eloquent champion of combining empiric and basic scientific approaches to HIV vaccine development. Her beliefs were based on a distinguished career of research on other vaccines, including live attenuated influenza, hepatitis, rotavirus and parainfluenza virus. As one example, her collaborative work with Brian Murphy of NIAID on the correlates of immunity for live attenuated influenza set a benchmark for clinical vaccine research addressing basic research questions.

Without question, Mary Lou had a unique ability to communicate to and advocate for volunteers enrolled in vaccine studies. Her insistence on what she believed was right could sometimes try her colleagues' patience, but her principled determination and integrity, her ability to focus on minute details while also looking at the broad history of vaccine development and her passionate concern for those at risk for HIV infection were just the characteristics that the field of HIV vaccine research needed, and continues to need.

We will miss her enormously.



*Pat Fast is the former Associate Director of the Vaccine and Prevention Program at NIAID's Division of AIDS (DAIDS) and currently Associate Director of Clinical Research at Aviron, Inc. Bill Snow is a founding board member of the AIDS Vaccine Advocacy Coalition (AVAC) and a member of the NIH's AIDS Vaccine Research Committee.*

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REMEMBERING MARY LOU CLEMENTS-MANN  
*continued from page 1*

"She was a strong advocate for ensuring that the needs of developing countries were addressed," says Peggy Johnston, IAVI's former Scientific Director. "Just weeks before the Swissair flight, Mary Lou submitted extensive reviews of IAVI's most recent funding applications," Johnston noted. "She cannot be replaced."

In addition to serving on the IAVI SAC, Clements-Mann was also a member of the UNAIDS steering committee for HIV vaccine

development, the U.S. CDC Advisory Committee on Immunization Practice, the FDA Vaccine Advisory Committee, and the Institute of Medicine Committee on the Children's Vaccine Initiative. She was also a principal investigator in the U.S. National Institutes of Health's AIDS Research Vaccine Evaluation Unit network.

Clements-Mann recently finished a manuscript, "Lessons from the Development of Other Vaccines," which will be published in an upcoming issue of *AIDS Research and Human Retroviruses*.

candidate HIV vaccine. (Abstract 31128)

Susan Barnett of Chiron presented data showing that immunizing guinea pigs with a DNA prime (expressing clade B *env* and clade E primary isolate *env*) and protein boosting (also clade B and primary isolate E) could generate high levels of antibodies that neutralize some laboratory and primary isolates of HIV. (Abstract 21196)

### Envelope glycosylation and neutralizing antibodies

In a study related to findings by Harvard researcher Ronald Desrosiers that deleting glycosylation sites from the SIV envelope could help generate more neutralizing antibodies (see *IAVI Report*, April-June 1998), researchers from Switzerland found that HIV-infected individuals whose viral envelope lacked key glycosylation sites produced more neutralizing antibodies to HIV. Conversely, patients with a higher number of glycosylation sites produced less neutralizing antibodies. The researchers concluded that differences in patterns of glycosylation in the viral envelope in HIV-infected individuals seem to correlate with development of neutralizing antibodies against laboratory strains of HIV. (Abstract 21131)

### Using DNA vaccines and cytokines

In a late breaker session, David Weiner of the University of Pennsylvania presented data showing that immunizing macaques with SIV DNA and a number of cytokine genes could increase specific types of immune responses (see *IAVI Report*, April-June 1998). Weiner's research team immunized macaques with DNA encoding HIV *env*, SIV *gag/pol* and different cytokines (IL-2, IL-4 and interferon alpha). Neutralizing antibodies to SIV were only seen in the IL-4 arm. The IL-2 and IFN-alpha had the highest level of CTL responses. At week 52, animals were challenged intravenously with non-pathogenic SHIV-IIIB. Approximately 50% of the monkeys in the

## Letters to the Editor

To the Editor:

I read your recent article on HIV DNA vaccines and the accompanying interview with Margaret Liu (*IAVI Report*, vol.3, no.3). The "startling discovery" of their 1993 report wasn't really quite so startling. We published an article in *Nature* in 1992 demonstrating the technology. It only seemed startling on reading the Ulmer, et.al. article in that they failed to reference that we had done so. In that article we referred to the technique as "genetic" vaccination which is technically accurate. I would advise you to be a little more careful in accepting company lines on these areas.

Dr. Stephen Albert Johnston,  
Director  
Center for Biomedical Inventions  
UT-Southwestern Medical Center

Letters can be submitted to: *IAVI Report*,  
810 Seventh Ave., 31<sup>st</sup> floor, New York,  
NY 10019 USA or to: [iavireport@iavi.org](mailto:iavireport@iavi.org).

IL-2 and IFN-alpha arms, but none of the monkeys in the IL-4 arm, were protected. Weiner concluded that, in this study, neutralizing antibodies were not a correlate of protection. (Abstract 21217)

### HIV BCG vaccine

Mitsuo Honda of the National Institute of Infectious Diseases in Japan reported that a recombinant Bacille Calmette-Gurien (BCG) vaccine encoding epitopes from the V3 section of the HIV envelope elicited CTLs and neutralizing antibodies in monkeys. Four of ten monkeys developed measurable CTLs and all ten developed neutralizing antibodies. Upon challenge with non-pathogenic SHIV-MN, four of seven animals were completely protected. All control monkeys were infected. Natural killer cell activity was detected in protected monkeys but not in the unprotected ones. (Abstract 33213) ♦

# IAVI REPORT

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NIH AIDS VACCINE PANEL MEETS  
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There was little public discussion about the ongoing search for a director of the NIH Vaccine Research Center. NIH Director Harold Varmus, who will make the ultimate decision, appears to be actively engaged in the committee's work, attending virtually all its scientific meetings. However, Varmus has still not been able to attract a top-level person to the post which was initially announced by U.S. President Bill Clinton in May 1997. ♦

## **Peggy Johnston Takes Key NIH Posts**

IAVI's Scientific Director, Peggy Johnston, has returned to the U.S. NIH to assume two key positions that will help oversee the agency's AIDS vaccine program. Johnston has been named to fill a newly created position, Assistant Director for HIV/AIDS Vaccines at NIAID, and will also become the Associate Director of the Vaccine and Prevention Program in NIAID's Division of AIDS (DAIDS). The appointments, according to IAVI's President Seth Berkley, "reflect what we believe are significant and encouraging changes at the NIH." He added that "Peggy has done an extraordinary job in jump-starting IAVI's scientific program and we are extremely grateful for the contribution she has made." In 1996, Johnston left her position as deputy director of DAIDS to become IAVI's first scientific director. Johnston, we are pleased to report, will continue to advise the *IAVI Report* on scientific matters.

## **IAVI Co-sponsors South African Workshop on Ethical Issues**

A workshop on ethical issues in HIV vaccine trials was held in Durban, South Africa on 1-2 September. The meeting was sponsored by the South African Medical Research Council, IAVI, the NIAID's HIVNET and the Fogarty AIDS International Research and Training Programme. Among the ethical issues discussed were: 1) obtaining informed consent from vulnerable, poorly-educated individuals; 2) obligations to promote HIV-prevention strategies among trial participants; and 3) obligations to provide care to trial participants. Another key issue that was considered: with clade C infection predominant in the region, should South Africa test a clade B vaccine or wait the estimated 2-3 years for a clade C-specific vaccine? South Africa has an estimated 2.9 million HIV-positive people and 1,700 new HIV infections each day.

## **Upcoming Meetings**

Two upcoming scientific meetings will include important discussions on AIDS vaccines. On 7-13 January, 1999, the Keystone Institute will sponsor a conference on AIDS vaccine research. The meeting, to be held in Keystone, Colorado, is chaired by Bruce Walker of Massachusetts General Hospital, Susan Buchbinder of the San Francisco Department of Health and Mark Feinberg of Emory University. For information contact: 1-970-262-1230 or [www.symposia.com](http://www.symposia.com).

On 31 January - 4 February 1999, the 6th Meeting on Human Retroviruses will be held in Chicago. To date, vaccines have been largely ignored at Retrovirus Meetings. However this year, conference organizers have suggested that the topic will be more prominently featured. (The preliminary program includes a symposium on live vector vaccines, but little else.) For more information contact: 1-703-716-7348 or [www.retroconference.org](http://www.retroconference.org).

## **U.S. NIAID to Assist with VaxGen Trial**

NIAID announced in September that it would collaborate with

VaxGen on the company's recently launched Phase III HIV vaccine trial in the U.S. The Institute is currently negotiating with VaxGen about providing assistance in measuring immune responses generated by the gp120 vaccine (AIDSVAX) and studying volunteers who become HIV-infected. The collaboration may also include assistance in testing VaxGen products with other vaccines.

## **HIV Continues to Spread in India**

At least one percent of the population in five Indian states is now infected with HIV, according to data released by the country's National AIDS Control Organisation. Rates of HIV in the other states are believed to be between 0.1 percent to 0.4 percent. The statistics were compiled through the collection of 400 samples at 180 test centers.

## **New AmFAR Grants for HIV Vaccine Development**

The American Foundation for AIDS Research (AmFAR) announced in October that it will provide special targeted-research grant support for HIV vaccine development. The grants will be for awards of between US\$75,000 to \$150,000. Projects will have a one-year period of performance with the possibility of renewal for a second year. For more information contact: 1-212-806-1696 or [www.amfar.org](http://www.amfar.org)

## **New NIH Innovation Grants for Vaccine Research**

The NIH's AIDS Vaccine Research Committee has announced a new round of innovation grants. Applications targeting any area of scientific investigation in AIDS vaccine research are welcome; however, two areas are especially encouraged: 1) studies aimed at inducing and/or enhancing T helper cell and/or memory responses to HIV vaccine antigens; and 2) the design/development of live vector vaccine delivery systems including non-viral approaches, such as bacteria.

Grants are for a maximum of two years at US\$150,000 per year. Applications are due by 2 January 1999. The Innovation Program was created to bring new and novel vaccine concepts into study. For more information contact: 1-301-435-3756 or [www.niaid.nih.gov/dai](http://www.niaid.nih.gov/dai)

## **New Vaccine Approach: "Pseudotyping"**

Researchers at the University of Pittsburgh have developed a new potential HIV vaccine candidate: replication-defective HIV that is "pseudotyped" with a vesicular stomatitis virus. The "pseudotyping" approach essentially wraps the genes from one virus in the coat of another virus. The combined virus is still able to express HIV proteins but not reproduce. Mice immunized with the pseudotyped vaccine, showed evidence of HIV proteins two months post-immunization. The results were reported in *AIDS Research and Human Retroviruses* (20 September 1998). The Pittsburgh group is currently studying immune responses in monkeys inoculated with the pseudotyped vaccine.