IAVI REPORT

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Whole Killed AIDS Vaccines: Time for a Closer Look

by Patricia Kahn, Ph.D.

Four decades of experience with vaccines made from killed virus particles have shown them to be safe and effective against diseases such as polio, hepatitis A, rabies, typhoid fever and influenza. Yet paradoxically, this classical strategy has barely been explored for HIV–even with the research climate now favoring broader support for multiple vaccine approaches.

As a result, the basic principle of a whole killed vaccine – immunize with inactivated virions that cannot replicate or cause infection but look immunologically just like live particles – has still not been tested for HIV, although studies now in progress on HIV's simian relative (SIV) may soon give some definitive answers in monkeys. In the veterinary area, however, whole killed vaccines account for most of the (few) successful or experimentally promising vaccines against retroviral diseases (see accompanying article, page 4).

A whole killed (WK) strategy offers several theoretical advantages for an HIV vaccine. Inactivated HIV virions would present the immune system with a full set of viral proteins, ideally in a natural conformation, and should therefore elicit a broader response than vaccines based on only one or a few antigens. Moreover, vaccine "cocktails" made by mixing different inactivated strains (as with flu) might help achieve broad protection,

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IAVI Fast-Tracks Two Promising AIDS Vaccine Approaches

Invests US$9.1 million in two international partnerships; obtains intellectual property rights to ensure access

By Victor Zonana

LONDON - Moving to quicken the pace of AIDS vaccine development and help ensure vaccine access throughout the world, IAVI launched two innovative international HIV vaccine research and development partnerships. The Initiative agreed to invest US$9.1 million in the partnerships. The investments represent the two single largest AIDS research awards by a non-governmental organization in history.

The scientific partnerships will be pursuing two of the most exciting new vaccine technologies in the world. Both partnership agreements include unique intellectual property provisions to help ensure that the fruits of the research are made available to the public sector in countries where the need for an AIDS vaccine is greatest

At the London announcement, Clare Short, Britain's Secretary of State for International Development, noted that "a preventive AIDS vaccine must be produced and made available to developing countries. That is why the U.K. Department for International Development attaches so much importance to this work and has provided support to IAVI."

Seth Berkley, IAVI's President, said: "Our goal is not only to ensure the development of an

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Industry Insider

by David Gold

Wyeth Lederle to Start New Adenovirus Vector Study

The U.S. National Cancer Institute (NCI) is working with Wyeth Lederle Vaccines to initiate a Phase I trial of an HIV adenovirus vector vaccine. The vaccine will include pieces of HIV *env, gag* and *pol.* NCI researchers, who have been studying adenovirus vectors as AIDS vaccines for a number of years, expect the study to begin in six to nine months. In a study published in *Nature Medicine* (3:651-658.1997) and updated in the *Journal of Virology* (72:10275-10280.1998), the researchers demonstrated that an adenovirus vector could protect chimpanzees against HIV. Adenovirus has important advantages as a vector: It induces long-lasting immune responses, including significant CTLs and they are targeted towards the mucosal system. However, one concern is that a single immunization with adenovirus could create pre-existing immunity to the vector and limit the immunogenicity of additional immunizations. To overcome this, NCI researchers suggest that secondary immunizations could use vectors based on slightly different adenovirus serotypes.

Merck's AIDS Vaccine Program

After holding off on a human trial of a candidate HIV DNA vaccine in 1998, Merck & Co. researchers are apparently hoping to initiate Phase I trials of at least one and maybe two different HIV vaccines in 1999. Known for keeping a tight lid on his research program, Emilio Emini, Merck's highly respected director of antiviral research, presented some data on the company's HIV DNA vaccines at the Keystone Meeting on HIV Vaccines in January. (A full report on the meeting will be included in the next issue of the *IAVI Report*.) According to the data, one DNA construct appears to generate reasonably good CTLs in monkeys. Merck is also reportedly looking at MVA and at least one more vector. Emini will address the January 1999 meeting of the NIH's AIDS Vaccine Research Committee (headed by David Baltimore) in closed session. Merck officials report that the company is investing significant resources in its AIDS vaccine effort. And Emini, for his part, is playing an increasingly visible role at vaccine forums. Yet much of the scientific community, as well as influential U.S. AIDS groups, still has little clue as to the company's overall strategy and timetable.

PMC Compares Canarypox Vectors, Launches Lipopeptide Trial

A Phase I study comparing Pasteur Mérieux Connaught's two new canarypox constructs with its current lead candidate, ALVAC vCP205, is reaching the six-month point and observers are looking for clues as to which candidate will be proposed for a Phase III U.S. trial. Very preliminary data from the trial reportedly shows that the two newer constructs – vCP1433 and vCP1452 – are generating similar levels of CTLs. Of course, these results could change as the trial progresses. In addition to standard methods of measuring CTL immune responses, researchers will also use an ELISPOT assay to evaluate CTLs. An earlier study found that another PMC canarypox construct – vCP300 – failed to generate superior immune responses to vCP205. In related news, the company has received final regulatory approval from French authorities to initiate a trial of an HIV lipopeptide vaccine.

VaxGen's AIDSVAX Enrollment

VaxGen officials report that almost 1000 volunteers have been enrolled in the company's Phase III U.S. study of its bivalent gp120 vaccine (AIDSVAX®). Approximately 40 trial sites have now been established. The company is seeking to enroll a total of 5000 individuals at high risk for HIV infection via sexual transmission. NIH officials are currently negotiating with VaxGen to provide funding for immunological and virological studies related to the trial. VaxGen is also forming a national community advisory board to provide advise about the study. The company hopes to begin a Phase III trial of its B/E gp120 in Thailand in early 1999.

Australian Company Stock Soars on Fowlpox/DNA Data

Shares in Virax, a small Australia-based company, jumped 155 percent in one day after researchers reported in the *Journal of Virology* (72:10180-88. 1998) that they had protected monkeys from an HIV challenge with a DNA/fowlpox prime boost (see *IAVI Report*, vol.3, no.4). The researchers, from the Macfarlane Burnet Research Centre and two other Australian laboratories, hope to first test the DNA/fowlpox vaccine combination vaccine in HIV-positive individuals and then as preventive vaccine in HIV-negative volunteers. On 12 November 1998, when the data was published, Virax's total market capitalisation more than doubled to A$9 million. Its share price reached 75¢ before closing 35¢ higher at 57¢. Virax's chairman, Tom Quirk, believes that the new technology could be a platform for vaccines against a number of infectious diseases and cancers. The fowlpox vector was created by Ian Ramshaw of ANU, while the DNA component was designed by Emory University researcher Harriet Robinson. However, members of the Australian team now report that a HIV DNA vaccine developed by Apollon (now Wyeth Lederle Vaccines) may be used in the human trials. The Australian researchers also plan on immunizing monkeys with an SIV version of the vaccine combination and challenging with a pathogenic SIV virus. ♦

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given the wide variability of HIV worldwide.

Scientific and Safety Concerns

So far, a mixture of skepticism and concern has kept WK strategies outside the mainstream of HIV vaccine research. One is safety: WK vaccines still carry the stigma of the tragic 1955 incident when an early lot of Salk polio vaccine was incompletely inactivated, causing 260 cases of polio among vaccinees and their contacts. Since then, stricter controls and more experience among vaccine manufacturers and regulatory agencies have prevented another such episode among hundreds of millions of vaccinated people. But the fear still lingers, and brings with it big liability concerns for vaccine developers.

"We threw the baby out with the bath water and never gave whole killed vaccines a fair try."
– Ronald Montelaro

Doubts that the strategy would work for HIV also played a big role, dating back to some early, promising results that turned sour. In the late 1980s, several research groups showed that formalin-inactivated SIV protected macaques against a live challenge–but the protective response turned out to be directed at antigens on the human cell line used for growing virus, not at epitopes on SIV. Although later work showed some protective effect of WK-SIV grown in monkey cells, it failed to reverse the loss of interest.

At the same time, the success of the first recombinant subunit vaccine (against hepatitis B) raised hopes that this approach was the wave of the future. "There was a bright new world of molecular biology out there," is how John Oxford of the London Hospital Medical College describes the optimism of that time. "Why would anyone want to bother with old-fashioned things like whole killed vaccines?" The safety issue also weighed heavily in favor of subunit vaccines, which cannot directly transmit disease.

These factors also strongly influenced peer-review funding, says Ronald Montelaro of the University of Pittsburgh, who served on the NIH study section that reviewed HIV vaccine grant applications between 1989 and 1995, the last two years as its chairman. "There was such tremendous baggage left over from the fiasco with SIV that most reviewers thought you couldn't do anything useful with whole killed HIV. By 1992, researchers knew not to send in grants on whole killed HIV. Subunits were everything. We threw out the baby with the bath water [and] never gave whole virus a fair try."

Coming in From the Fringe

Montelaro is still convinced that "whole killed HIV is absolutely feasible and worth trying," a view that may be gaining ground as optimism about HIV subunit vaccines wanes and support grows for strategies that incorporate more of HIV's antigenic complexity. Another long-time champion of the approach is Burt Dorman, now at Acrogen, Inc. in Oakland, CA who made WK vaccines against many veterinary diseases but could never get support to work on HIV. Peggy Johnston, former Vice President for Scientific Affairs at IAVI and currently Assistant Director for AIDS Vaccines at the U.S. National Institute of Allergy and Infectious Diseases (NIAID), also sees WK as an approach that "must be tried."

What's more, some of the scientific hurdles look less serious than they once did. The early finding that HIV easily sheds its envelope – which created the impression that it would be difficult to inactivate HIV yet keep the virions intact – turned out to be true only for some strains, not for others. And the belief that WK vaccines stimulate antibody responses but not cellular immunity (which may be essential for protection) is now clearly contradicted by studies of WK vaccines for HIV-related animal viruses.

Yet there are still obstacles. Aside from liability concerns, industry sees poor potential for profit from a vaccine made with decades-old technology that is unlikely to generate patents. Nor can most university scientists afford to get deeply involved, since their funding and academic success depend on answering fundamental questions, not on the type of empirical research needed to make a WK-HIV vaccine candidate: systematically searching for ways to inactivate HIV without destroying its immunogenicity; working out doses, immunization routes and adjuvants; and developing methods for producing huge quantities of virus safely and economically.

All this has left only a handful of groups actively working on preventive WK-HIV vaccines (interestingly, none of them funded by peer-reviewed government grants). Another effort – that of Martha Eibl's group at the Vienna-based Immuno AG – ended in 1997, just prior to the first planned primate tests, when the company was sold and all AIDS vaccine work discontinued. (Several groups are working on designing less-than-whole virions, efforts that are not discussed here.)

The most advanced WK approach, in terms of monkey studies, appears to be that of the U.S. National Cancer Institute's (NCI) AIDS Vaccine Program, led by Larry Arthur in Frederick, Maryland. Their approach emerged from years of study by other NCI researchers on the "zinc finger" region of HIV's nucleocapsid protein, which is crucial for viral infectivity. That work led to the finding that aldrithiol-2 (AT-2), a chemical which binds to these zinc fingers, effectively kills the virus, but seems to spare proteins on the virions' outer surface. NCI researchers led by Jeff Lifson recently demonstrated that the surface proteins of AT-2-treated-HIV are not detectably altered, either functionally or conformationally. Other new work has shown that AT-2-treated-SIV virions also retain their surface properties, and that the inactivation process can be scaled up to large volumes.

Studies of AT-2-inactivated SIV in macaques are now underway. In one experiment designed to probe the crucial safety issue of whether inactivation is complete and irreversible, two monkeys were infected with huge amounts of AT-2-treated SIV (roughly equivalent, says Arthur, to enough HIV to infect everyone in the U.S.). The monkeys are still disease-free after four months, and continue to be followed. Protection experiments on 20 animals are also ongoing and should yield preliminary results in early summer. Also planned

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Whole Killed Vaccines for Animal Retroviruses Show Promise, Yield Clues About Correlates

by Patricia Kahn

Although HIV researchers have all but ignored strategies based on inactivating intact virus particles (see story page 1), such "whole killed" (WK) vaccines have shown some clear successes against retroviral diseases in the veterinary world. What's more, these animal systems provide useful models for analyzing both natural and vaccine-induced immunity to lentiviruses (the class of viruses that includes HIV, SIV and FIV) in their normal hosts.

The clearest proof that inactivated virions can protect against retroviruses comes from the feline leukemia virus (FeLV), a retrovirus that can cause fatal immuno-suppression, anemia, leukemia and lymphoma in infected cats. Several different WK vaccines have come onto the market since the mid-1980s, with the best one reportedly showing over 90% efficacy. A subunit vaccine made from a portion of the FeLV envelope protein is also commercially available, but some reports suggest it is slightly less effective.

Studies with HIV-like animal viruses clearly contradict the dogma that whole killed vaccines generate antibodies, but no cellular immunity.

Little is known about how the FeLV vaccines work, since most research pre-dates the availability of certain key assays and reagents, including those to analyze cellular immunity in the cat. Ed Hoover of Colorado State University, who developed the newest WK FeLV vaccine, says that immunization with only a few doses can effectively protect the animal. Interestingly, some vaccinated cats do not appear to develop detectable neutralizing antibodies until after challenge, although they are clearly protected, leading Hoover, among others, to suggest that cellular immunity probably plays an important role. He is now going back to test this theory in the protected cats.

Yet, although it provides proof of principle, FeLV appears to be a relatively easy retroviral vaccine target, since some animals naturally resist infection completely, while others recover after only a transient infection, with both scenarios resulting in lifelong immunity. Another simplifying factor is that FeLV strains show only minor antigenic differences in their envelope protein, amounting to less than the variation within a single HIV clade.

A much closer HIV relative and potentially more useful model for HIV vaccinologists is the feline immunodeficiency virus (FIV). Like HIV, FIV is a lentivirus that shows enormous antigenic variation in the envelope, with five clades identified so far. It also causes a disease quite similar to AIDS in humans, starting with an acute infection followed by a long, usually asymptomatic phase (typically 4-5 years but as long as 10) that ends in a fatal deterioration of the immune system.

No licensed vaccine exists yet for FIV, but among the many experimental approaches being studied, WK so far appears to be the most effective. (Live attenuated also seems to protect; canarypox vectors work only with a WK boost and confer less long-lived immunity; new DNA vaccines show some promise and envelope subunits actually enhance disease.) The well-studied WK-FIV vaccine developed by Janet Yamamoto at the University of Florida in Gainesville is made from paraformaldehyde-inactivated virions of a low-pathogenic, clade A strain. While the vaccine is effective against the homologous virus and its close relatives, it does not protect against other, more virulent FIV subtypes. But Yamamoto's newest version, a "cocktail" of inactivated virions from clades A and D, seems to induce broader protection, conferring long-term immunity against primary isolates of clades A, B and D. (Strains from the C and E subtypes have not yet been tested.)

This new vaccine came about only after much systematic tinkering, says Yamamoto. A key factor was the choice of virus strain. She initially began with three different strains and found that one was "completely useless" as an immunogen, one was mediocre and one was highly effective. Another crucial ingredient was a high-producer cell line for growing virus, something she had developed for the original clade A vaccine and then further exploited using a simple proprietary method that allowed her to infect the cell line with FIV subtypes it normally resists. Commercialization of the vaccine is now underway.

Studies of vaccinated cats have shed some light on what immune responses correlate with protection. Initially the best correlate appeared to be high levels of neutralizing antibody, says Oswald Jarrett of the University of Glasgow. But it later emerged that the levels decline gradually over the year after vaccination and that long-term immunity seems to reside with CD8+ CTLs, especially those directed at the envelope protein and, according to Yamamoto, also at *gag*. The finding that this WK-FIV vaccine generates protective CTLs is a crucial one, since it contradicts the dogma that WK vaccines stimulate humoral immunity but not the critically important cellular responses.

A WK strategy is also proving successful against another lentivirus, the equine infectious anemia virus (EIAV). Like HIV and FIV, EIAV has a highly variable envelope (although not enough sequencing has been done to define clades), yet the experimental vaccine developed by Ronald Montelaro at the University of Pittsburgh and now being commercialized confers broad protection

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An Interview with Neal Nathanson

In May 1998, Neal Nathanson, M.D. was appointed director of the U.S. NIH's Office of AIDS Research (OAR). Nathanson was chair of the University of Pennsylvania's Department of Microbiology from 1979-94 and authored one of the seminal textbooks on virology. In the short time that he has held the OAR post, Nathanson has established a reputation for being blunt, pragmatic and deeply committed to the development of a safe and effective AIDS vaccine.

IAVI Report: What are your priorities on AIDS vaccine research?
Neal Nathanson: I'm particularly concerned about the gap between taking good ideas from the lab and moving them into human trials. NIAID is going to use rhesus monkeys to screen many vaccines as to their relative efficacy since you can't put everything into human trials. Then we'll move the most promising ones into human trials.

IAVI Report: Are we putting too many eggs in the rhesus monkey model?
Nathanson: There are mixed views about how well the primate model can predict the merits of candidate vaccines. You can't anticipate the exact efficacy in humans, but by testing candidates against similar challenges, we can compare them. We'll use a standard series of challenges, graded from a mild (intravaginal or intrarectal) to a severe (intravenous) challenge.

IAVI Report: Will the companies put their candidate vaccines into these comparative studies?
Nathanson: Some are interested, others may worry that comparative tests might dampen enthusiasm for their product. The investigators will initially test DNA, MVA, vaccinia and a canarypox construct. We'd like to test the canarypox/gp120 prime boost, because by comparing human and primate results, we'll learn more about how useful these models are.

IAVI Report: Recent studies show that in some cases, recombinant vector vaccines can protect against SIV challenge in monkeys.
Nathanson: The VEE and vaccinia vectors are clearly showing promise. But with the vectors, safety and manufacturing issues could be a big factor. The FDA may have inadvertently set a high standard for licensing, because they now consider vaccinia to be borderline, as to safety. But with smallpox vaccines the rate of fatal complications is about one in a million. If this is marginal, how will FDA accept something with slightly more risk?

There are some real gaps in the NIH program. These are beginning to be addressed.

IAVI Report: Does the promise of these vectors make a human trial of a live attenuated HIV vaccine unlikely?
Nathanson: Yes. I can't imagine such in a trial within the next five years. A safe, effective live HIV vaccine may ultimately be developed, but we don't currently have the knowledge to do it. From the data I've seen, Ron Desrosier's Delta-4 construct does not protect against IV challenge. Against a vaginal challenge, there was modest protection. And there are safety concerns. So these constructs may not fall into the magic window of being protective and safe.

Ron wants to start a large-scale trial in monkeys and I support this because it may be possible to formulate a lentivirus that infects without causing disease. Chimpanzees can have robust HIV infections without disease. And SIV does not cause disease in some monkeys. If we knew why, we might be able to formulate a safe, live HIV vaccine.

IAVI Report: Are you satisfied with the level of private sector interest in AIDS vaccine development?
Nathanson: Clearly, we cannot rely on the private sector alone to develop an AIDS vaccine. But the pharmaceutical companies were never created to serve the public in quite that way. Almost none of the vaccines now on the market were developed by big companies. They are not behaving differently than their historical tradition. So getting up on a bully pulpit and beating on them is not appropriate.

IAVI Report: But there are companies like SmithKline Beecham, the world's largest vaccine company, that appear to have very limited AIDS vaccine programs.
Nathanson: You're ignoring history, because they didn't develop any of the vaccines they're now making.

IAVI Report: But big companies can play a role in doing critical basic research. Look at the contribution Merck made with its basic research on the HIV protease enzyme.
Nathanson: I'm not saying that they will not contribute anything. Corporate culture is not a monolith and some companies have decided to take this on. We must encourage them. That's why NIH is paying for so many studies. But much of the basic and some applied research will be done outside of the companies. That's the history of the Salk and Sabin vaccines. They were developed in small labs. When they were shown to be safe and effective, the big companies took over and produced the vaccines.

IAVI Report: You've said liability is a big issue.
Nathanson: My initial sense is that industry is concerned about liability. The insurance costs a lot, and, within the U.S., the cost of a lawsuit, even a frivolous one, can be enormous. So it has a real chilling effect on vaccine development.

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IAVI Report: How do you address the issue?
Nathanson: Historically, the U.S. government has acted as the insurer. That was done in 1976 with the swine flu vaccine when manufacturers refused to produce it. Congress passed a law that essentially assumed liability. The government paid the costs whenever there was a judgment. So there are precedents for government taking on liability for producing vaccines.

IAVI Report: Even if a vaccine was effective, how would you get it to billions of people?
Nathanson: That's not a trivial problem, but, frankly, I am so concerned about finding a product that shows evidence of being protective — that that's where I'm focused. My sense is that once we have a proof of principle and a product that can be scaled up, the resources will be found.

A lot of vaccinology is trial and error. Vaccines were made, they worked and we really didn't understand all the science.

IAVI Report: Why do you think VaxGen's Phase III trial has been controversial?
Nathanson: I wasn't involved in the 1994 decision (not to go ahead with a Phase III gp120 trial) and to keep looking back distracts people from a more productive pathway. Now, is it worth investing US$25 million for a product which may be of marginal value?

Well, that decision has been made, because VaxGen, to their credit, raised the money in the private sector. So NIH — and I'm just a new boy on the block — wants to obtain the maximum amount of information from the trial. Peggy Johnston is leading the negotiations. But I'm concerned that the FDA accepted VaxGen's plan for the outcome measure to be infection vs. no-infection because even if the vaccine doesn't prevent infection; it could down-modulate it.

IAVI Report: Will the U.S. study be able to determine whether the vaccine delays or even accelerates disease progression?
Nathanson: I don't think so. Unfortunately, the trial may conclude that there was no statistical difference in rates of infection, but not detect whether the vaccine impacted viral setpoints (the level at which viral levels "plateau" after infection). So, that's the kind of thing where I'm focusing my energy, and not on rehashing why Tony Fauci and Ashley Hasse did something four years ago.

IAVI Report: Blood samples will be taken every six months. Wouldn't it be better to do it every three months?
Nathanson: My intuition is that three months would be safer. But there are practical issues about how many samples you can collect and store. And in industrialized countries, as infections are detected, treatments that alter the course of infection will be offered. So the trials may depend on surrogate markers: viral load and, secondly, CD4 counts.

IAVI Report: Is viral setpoint a sufficient surrogate for disease progression?
Nathanson: That's a very important question. I'm pushing for a meta-analysis of all monkey experiments where viral setpoints have been followed to determine the relationship between setpoint and disease progression. In human studies, the higher the setpoint, the shorter the survival. But do these survival curves apply in the context of a vaccine? And does a vaccine that reduces the setpoint simply prolong the incubation period or provide permanent protection from disease? We don't know.

IAVI Report: What is your sense of a possible correlate of protection?
Nathanson: My working view is that there is no holy grail or sole correlate of protection. So I would put it this way — an immunogen that raises some neutralizing antibody and CTL response against a variety of viral proteins is going to be better than an immunogen that relies exclusively on one response. My guess — although I'm not an immunologist — is that those things are not in sharp competition, and that the right immunogen could do both simultaneously and thus be more likely to protect.

IAVI Report: How much is NIH spending on AIDS vaccine research?
Nathanson: For fiscal 1998 we spent in the range of US$150-200 million. And each year we're pushing that up by a lot higher than the annual increase in overall NIH spending.

IAVI Report: President Clinton announced that US$33 million was added to the AIDS vaccine budget. Where will that go?
Nathanson: A lot of it is going into clinical trials of vaccines, the expanded primate model system and to more investigator-driven innovation grants.

IAVI Report: What about the vaccine center at NIH?
Nathanson: The good news is that construction of the building has started and it should be open in 2000 with a capacity for 130 people. But frankly, we've had trouble finding a top level candidate for the position. Harold Varmus (NIH Director) has been extremely successful in recruiting very good people, in spite of the limitations in working for government. There are a variety of reasons why people turned the position down.

IAVI Report: Money is probably a big factor. How much did you offer?
Nathanson: Well, you can't make more than the President, which is US$200,000 a year. NIH has done a remarkable job of improving salaries, but the best candidates from industry are making three times higher for this kind of a job.

IAVI Report: It's been almost two years since the NIH AIDS Vaccine Advisory Committee, headed by David Baltimore, was created. You were a member of the committee. What has it achieved?

Nathanson: I would rather leave it to David to give you an assessment of that, but my sense is the committee has accomplished several things. It has raised the general level of interest, enthusiasm and budgetary support for vaccine development. That's certainly not trivial. And it's happened primarily because of David's prestige.

It has also led to establishment of the NIH vaccine center and to the Innovation Grants Program that has supported a groundswell of basic research and attracted new investigators to the field. And the committee has had an ongoing dialogue about the scientific issues. That's made a real impact in sharpening thinking about research required to pave the way for a vaccine.

I can't imagine a human trial of a live HIV vaccine within the next five years.

IAVI Report: Are there any areas where the committee's progress has been disappointing?

Nathanson: One thing that the committee has not chosen to do, which I think is important, and which we did in the OAR council meeting last October (see story below), is to look at the NIH program from the point of view of a vaccine development program, and really critique the system, in addition to the scientific issues.

And without being critical, there are some real gaps in the program at NIH, which are now being recognized. The committee has not really focused on these, particularly. They include the provision of facilities for production of candidate vaccines and development of a primate system to compare vaccine candidates. The Baltimore committee supports these. But it hasn't used its bully pulpit to push them aggressively.

IAVI Report: The NIH is recognized for its basic research. Can it do the applied research necessary to develop an AIDS vaccine?

Nathanson: NIH does extremely well at investigator-initiated, curiosity-driven research, and even research that is somewhat applied. But if you compare it to a leading pharmaceutical company with a major research and development program, you'd obviously see differences. The companies are designed to bring products to market. Their programs are run in a paramilitary style, with a few top people making decisions and pushing things along. They don't have the cumbersome process of putting out program announcements, peer-reviewing them and awarding grants. It's more controlled, so there's less creativity. But it's much better at answering directed questions.

IAVI Report: Can NIH take on some of those characteristics in the applied area?

Nathanson: That's hard to say. Attempts are being made. NIAID is crafting programs to do these things, although traditionally this

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OAR Advisors Meet to Discuss AIDS Vaccine Effort

By Sam Avrett

On 14 October 1998, the Office of AIDS Research Advisory Council (OARAC) reviewed the NIH's AIDS vaccine research program. It was the first OARAC meeting to focus entirely HIV vaccine research. Chaired by newly appointed OAR head, Neal Nathanson (see interview, page 5), the gathering also featured the debut of Peggy Johnston in her new role as NIAID's Assistant Director for AIDS Vaccines.

The OARAC is comprised of AIDS researchers, community advocates, and industry officials. Also attending the meeting were representatives from many branches of the U.S. government, not-for-profit organisations and research institutions.

Key areas of discussion and debate included:

A Call for Movement on Vaccine Research Center (VRC) Director

While construction on a US$26 million Vaccine Research Center began in September 1998, OARAC members were clearly concerned that a director had still not been hired, despite an 18-month search. Although the search committee reached out to individuals with expertise in basic science and product development, the position remained unfilled at the time of the meeting. The OARAC recommended that the job qualifications be somewhat loosened, and that the NIH Director speak directly with leading prospects to assess what aspects of the job were making it unattractive.

Questions About NIAID's AIDS Vaccine Program

The Council raised a number of questions about NIAID's AIDS vaccine program. These include: Would the new programs offer enough funding and few enough strings to bring in industry partners? Can NIH steer its academic research to conform better to industry development requirements? Are NIH-funded researchers encouraged to work with industry partners? What is NIAID doing to ensure that its vaccine development is linked with other prevention efforts? Johnston, in her new role as head of NIAID's AIDS vaccine program, is expected to lay out some of her thoughts and plans at the next meeting of the NIH's AIDS Vaccine Research Committee.

Plans for Comparative Primate Studies

For years, there has been widespread concern about the conflicting and limited research results coming from scattered, non-standardized primate studies of candidate vaccines. A new NIAID initiative seeks launch a large, comparative macaque trials of various vaccine concepts by March 1999. The trial would involve 100 macaques, one pathogenic SHIV challenge virus, and would compare several vaccine concepts (vaccinia vector, modified vaccinia Ankara (MVA), canarypox

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Live Attenuated AIDS Vaccines Debated at London Forum

By Julian Meldrum

On 1 October 1998, London's Royal Free Hospital Centre for HIV Medicine sponsored a lively debate on the issues surrounding testing live attenuated (weakened) HIV vaccines in humans.

The idea for such studies has been proposed by the U.S.-based International Association of Physicians in AIDS Care (IAPAC) and has aroused significant media interest and scientific controversy.

IAPAC officials have argued that individuals with a high-level of knowledge about HIV – such as physicians – should be allowed to take a calculated risk that might not be acceptable for others. They propose that a trial be conducted with a vaccine designed by Ronald Desrosiers of Harvard University. The vaccine would consist of HIV with sections of genetic material, including the *nef* gene, deleted. These attenuated viruses have so far shown the strongest protective effect of any vaccines against SIV, the monkey equivalent of HIV. And so, they have proposed human testing of an HIV vaccine modeled on these SIV vaccines. Even if the experiment went wrong, IAPAC argues, there are now HIV treatments available from which trial volunteers could get maximum benefit.

Despite the scientific questions, IAPAC's proposal clearly injected some much needed attention to AIDS vaccine development.

The debate was chaired by Richard Horton, editor of *The Lancet*, and held at the Royal College of Physicians in Regent's Park, London. Horton described the development of an HIV vaccine as one of the greatest challenges in medicine today.

Jose Esparza of UNAIDS outlined the need for an AIDS vaccine and the approaches currently being investigated. According to Esparza, in the next ten years, efficacy trials could be completed for at least three approaches, which might then lead to partially effective vaccines.

Strong opposition to human trials of live attenuated HIV vaccines was expressed by Ruth Ruprecht of the Dana-Farber Cancer Institute in the U.S. She described experiments her research team had conducted on newborn rhesus monkeys, while trying to find a vaccine that could protect them against SIV. The live attenuated vaccine turned out to cause AIDS. Ruprecht concluded that using a weakened form of HIV, even so weak that it could not protect a challenge, would still be too risky for human trials. The Dana-Farber researcher did not rule out all attenuated versions of HIV as vaccines, but said that until scientists understood exactly what makes HIV so pathogenic, such a vaccine was too risky.

Jennifer Learmont of the Australian Red Cross Blood Transfusion Service in Sydney provided new information on a group of people with HIV who were apparently infected with a defective (*nef*-deleted) form of HIV up to 17 years ago and have remained well without antiviral treatment. However, some of these individuals are now showing signs of immune suppression.

The ethical issues raised by the IAPAC proposal were discussed by one of the U.K.'s pioneers in AIDS research, Anthony Pinching of St. Bartholomew's Hospital. According to Pinching, ethical guidelines for human research are largely based on the idea that the investigator knows more about the issues at stake than the research subjects. What, then, if this is not the case? What if trial participants know as much, or more, than those doing the research? The textbooks do not address this possibility.

However, it is still unclear as to how truly voluntary participation in a live HIV vaccine trial might be. In a perceived emergency, with powerful peer pressure, participants might misjudge the situation.

Finally, Michael Youle, a London physician, explained why he volunteered to participate in a live attenuated HIV vaccine trial. Other live attenuated vaccines, he explained, are in widespread use, including at least one (against varicella) for which, he claims, there remains uncertainty about long-term safety issues.

However, Youle now suggests something slightly different from the IAPAC proposal: the possibility of using a live, weakened strain of HIV as a challenge virus to test the effectiveness of other, safer, candidate vaccines. And he argued that it might be reasonable in some volunteers, such as those dying of terminal illnesses, to test live HIV vaccines, just as Edward Jenner injected a vaccinated child with smallpox virus, two hundred years ago. (University of Massachusetts researcher John Sullivan recently proposed to test a live HIV vaccine in volunteers who have untreatable cancers, but intact immune system.)

One member of the audience suggested that if the experiment went wrong, it could cost the lives of some of the most committed HIV doctors. Youle observed that he often flies with many other AIDS doctors on his way to scientific meetings and "as a gay man and as an HIV doctor I am in continual risk of HIV."

UNAIDS would not at this time support conducting human trials of live attenuated HIV vaccines candidates in developing countries, according to Esparza. And even if a live attenuated virus appeared safe in volunteers in industrialized countries, argued Ruprecht, it would not necessarily guarantee safety in a population exposed to malaria, tuberculosis and other pathogens.

The last word went to Pinching, who suggested that, despite the scientific questions, IAPAC's proposal had clearly achieved something important: it injected some much-needed attention and urgency to the need for development of a safe and effective AIDS vaccine. ◆

Julian Meldrum is editor of the London-based Body Positive Newsletter

US Army's AIDS Research Budget Cut 40%

Congress fails to provide supplemental funds; Army vaccine efforts may be curtailed

By David Gold

The U.S. Department of Defense's AIDS research program was effectively cut by nearly 40% when Congress failed to provide the Walter Reed Army Institute for Research (WRAIR) with US$15 million in supplemental budget funding. According to observers, this is the first time in recent memory that the program has failed to receive a supplemental appropriation.

The move surprised and disappointed vaccine advocates. "We were dismayed to learn that the Army program did not receive any supplemental funding," said Sam Avrett of the AIDS Vaccine Advocacy Coalition.

In fiscal years 1997 and 1998, WRAIR received almost US$40 million – $23 million in basic funding and a supplemental appropriation of $15 million. Congressional sources report that for 1999, WRAIR received $24.4 million as it had requested, but no supplemental funding. Most of the $15 million decrease in 1999 will come from the HIV vaccine budget, according to Avrett.

David Baltimore, who heads the NIH's AIDS vaccine advisory committee, also expressed disappointment at the cutback. Baltimore had met with WRAIR officials last year to discuss their AIDS vaccine program, and was reportedly impressed with the program. Ironically, the cut came to light in the same week that U.S. President Bill Clinton announced that the NIH was receiving an additional $33 million for AIDS vaccine research.

WRAIR's vaccine program is focused almost primarily on developing and testing candidate AIDS vaccines. The Institute works closely with a number of key vaccine manufacturers, most notably Pasteur Mérieux, Wyeth Lederle and Chiron. WRAIR also has a history of providing funding for vaccine development at other institutions, including early work on peptide vaccines at the U.S. National Cancer Institute and on VEE replicon vaccines at the University of North Carolina/AlphaVax. (The latter recently received a $4.6 million investment from IAVI.)

WRAIR's extensive network of international trial sites are considered a valuable resource in testing candidate vaccines. The Institute's collaborative efforts with the Thai government and researchers, for example, helped pave the way for a number of AIDS vaccine trials in that country. WRAIR is currently supporting Phase I trials to evaluate DNA, live vector and oligomeric envelope protein vaccines.

According to Avrett, approximately 54% of the WRAIR budget goes to direct AIDS vaccine research. Another 16% goes to other international prevention, which includes global surveillance of the epidemic, changes in incidence rates, and recombination of virus – all of which are useful in preparing for vaccine trials. Without the supplemental funding, the vaccine program, and in particular the international clinical trial development programs, face significant cutbacks.

IAVI's Seth Berkley voiced strong support for WRAIR's AIDS vaccine program. "The Army's focus is on moving candidate vaccines into human studies, working closely with industrial partners and investing resources in building international testing capabilities. We are very concerned that this important program has been cutback."

Researchers, advocates and congressional supporters all suggested that, in the future, they would pay closer attention to the WRAIR budget and appropriation process. "We will work hard to make sure that this does not happen again," says Avrett. ◆

January 1999

To Our Readers:

We would like to let you know of some changes at the ***IAVI Report.***

As we continue to grow – our readership now includes more than 10,000 researchers, public health and government officials, industry scientists and community advocates in 98 countries – IAVI is expanding its commitment to the publication.

Towards this end, we have hired Patricia Kahn, Ph.D. as associate editor. Patricia previously served as a contributing correspondent for *Science*, based in Australia and then Germany. She is a geneticist by training and before becoming a journalist, worked in the European Molecular Biology Laboratory in Germany.

With Patricia and a growing core of researchers and advocates now contributing to the publication, we will be moving to a bi-monthly production schedule, starting with our next issue. This will allow us to provide additional and more timely coverage of international AIDS vaccine research and development issues.

IAVI is fully committed to making this publication the most credible and vital source of global information on AIDS vaccines. We will also continue to use it as a platform to highlight gaps in AIDS vaccine development and advocate for an expanded international research effort.

In the near future, we will also be expanding our use of online technology to distribute AIDS vaccine and IAVI-related news. If you would like to receive such information and we do not have your current e-mail address, please send it to us at iavireport@iavi.org. We also ask that you send comments and suggestions about the publication to this address.

Overall, the past year was one of extraordinary progress and growth for IAVI and the *IAVI Report*. We thank you for your continued readership and support and wish you a healthy, happy and peaceful 1999.

Seth Berkley
President, IAVI

David Gold
Editor, *IAVI Report*

Conducting AIDS Research in Kenya: An Interview with Omu Anzala

Omu Anzala, M.D., Ph.D. is a researcher at the University of Nairobi and Oxford University, and is part of an IAVI-sponsored research team developing an HIV DNA/MVA vaccine that will be tested in the U.K. and Kenya. Anzala, currently based in Nairobi, is also studying a group of Kenyan sex workers who are infected with HIV, but show no sign of disease.

IAVI Report: Can you tell us about your research?
Anzala: We are developing a DNA/MVA combination of HIV vaccines that will be tested in the U.K. and here in Kenya. We have some promising data in mice and monkeys and we are now building the infrastructure to do Phase I trials.

IAVI Report: When do you expect the trial to start?
Anzala: We hope to begin our Nairobi trial in the year 2000, by July.

IAVI Report: Aren't the vaccines based on strains in the Kenyan population?
Anzala: Yes. We have been looking at various cohorts in Kenya. And part of that work has been to characterize the HIV subtypes prevalent here. We now know that 70% of our patients here in Nairobi are infected with clade A strains. The rest are distributed between clade C, D, and F. The vaccine we have designed takes this into account.

The impact of the epidemic is beginning to hit and our healthcare system won't be able to handle it.

IAVI Report: Do you anticipate any difficulties in getting the trial approved or enrolling participants?
Anzala: Because of the launch in London, news about the trial has already filtered in here. The interest is there and I don't think that we are going to have major difficulties. Our proposal is already submitted to the Kenya National Hospital Ethical Committee. We have also been talking with the Director of Medical Services and other organisations that have an interest in this.

IAVI Report: Can you tell us about the state of the AIDS epidemic in Kenya?
Anzala: We believe that HIV was introduced in Kenya during the 1980s or thereabouts. The first patient to be diagnosed with HIV/AIDS was in 1985. And the latest figures indicate that 1.5 million people in Kenya are infected with HIV, out of a population of 26 million.

IAVI Report: Is it leveling off?
Anzala: No, it continues to grow. Initially, the epidemic was focused on people 25 years and older. But now the epidemic is beginning in 18-25 year olds and moving into the smaller, rural communities.

IAVI Report: Is there a significant AIDS prevention effort underway?
Anzala: There are organizations that provide education and advise people on prevention. These efforts are important and must continue.

IAVI Report: Have the full effects of the epidemic impacted the healthcare system yet?
Anzala: The impact is beginning to be felt. About 60-70% of the medical wards bed occupants at Kenya National Hospital are now HIV-infected. And in another two or three years, we'll have a huge problem because the healthcare system cannot really handle it.

IAVI Report: You are also studying the cohort of sex workers in Kenya.
Anzala: Yes. My work has been looking at the natural history among this high-risk group. We are concentrating on a small sub-cohort of these women who have been infected with HIV for at least 12 years and have remained asymptomatic. I've been looking at their immune systems, the subtype they're infected with and genetic markers, to try and find the mechanism behind their long-term survival.

IAVI Report: What percentage of the cohort are long-term non-progressors?
Anzala: We are following just over two thousand women in our cohort. And sixty of these are long-term nonprogressors.

IAVI Report: And what do you attribute this to?
Anzala: We haven't found any definitive genetic markers yet. The only thing that we did find within some women is a high frequency of what we call a 64-I mutation, which may be linked to certain promoters in the CCR-5 gene. And across the board, we've found these women to have high levels of CTLs. This could be why they survive longer.

IAVI Report: I've heard that a couple of the exposed but uninfected Kenyan sex workers have become infected after stopping their work.
Anzala: That is true. Our thinking is that if they continue prostitution, there is continuous antigen stimulation, and that may keep the CTLs at heightened levels. But when they stop, there's no antigenic stimulation, which results in diminished immune responses. So if there is exposure they get infected.

IAVI Report: Isn't that a little worrisome, since it may suggest that we need constant, long-term immunizations to protect people?
Anzala: No, I don't think so, because with the vaccine we are thinking of — DNA and MVA — our hope is that the CTLs will be at much higher levels for long periods of time. In our immunized monkeys, eight months after the last immunization, there were still quite reasonable levels of CTLs present.

IAVI Report: Other researchers have found that the resistant Kenyan sex workers have high levels of HIV IgA antibody in the mucosal secretions.
Anzala: Yes, we are working with Rupert Kaul on this. We have always felt that there must be a level of protection at the mucosal level. But mucosal immunity has not been researched very well. So we looked at the mucous membranes. And we found that these women have HIV-IgA in their genital secretions, as well as mucosal HIV-specific CTLs.

IAVI Report: What percentage of sex workers in Kenya are infected with HIV?
Anzala: When we began this work, fifty to sixty percent were infected. But that's gone up to over ninety percent.

IAVI Report: If a woman began as a sex worker in Nairobi, how quickly would you expect her to become infected?
Anzala: We consider a sex worker to be exposed but uninfected if she has remained HIV negative for at least three years. But by about six months, most are already infected.

IAVI Report: How many potential HIV-exposures does the typical sex worker have per day?
Anzala: They see approximately seven to eight clients per day.

Using local strains for these vaccines shows that they were made with our people in mind and not just for somebody else.

IAVI Report: And do you have any sense of what percentage of those are using condoms?
Anzala: It has increased somewhat, when we started the cohort in 1983 condom usage was below fifty percent. Now over eighty percent of the cohort use condoms at different times. They are provided free at clinics we run.

IAVI Report: Has there been reaction to the announcement about the IAVI-sponsored vaccine trials in Kenya?
Anzala: The reaction has been positive. There has been a lot of interest. The biggest questions people have are: when do we plan to begin and who are we going to vaccinate? We hope, through a series of TV and print interviews, to make clear exactly what the vaccine development involves.

IAVI Report: Has the government been cooperative?
Anzala: Yes, very cooperative. In fact, the Director of Medical Services attended our vaccine seminar.

IAVI Report: In some developing countries, it hasn't been easy getting AIDS vaccine trials launched. Do you have any sense of how Kenya will turn out?
Anzala: So far, I've been able to talk to quite a number of medical groups and everybody is quite positive. But we have to make sure that we go through all the regulatory bodies, and that is exactly what we are doing. We are aware of the problems getting a trial started in Uganda. But there is no way will know if this works unless we go ahead and test it. And we've already had some bad publicity in a few local dailies. They have suggested that we intend to use Kenyans as guinea pigs. We hope that once we begin to disseminate the information this kind of bad media will be pushed aside.

IAVI Report: Will it help you that this is actually a collaboration between U.K. and Kenyan researchers?
Anzala: Definitely, because it will not be seen as if somebody developed the vaccines somewhere else and then just decided to test them in Kenya. We've been collaborating with Oxford for a long time in developing an HIV vaccine. We are part and parcel of the process.

IAVI Report: So long-term scientific collaborations really make it easier to initiate these trials?
Anzala: Much, much easier, because then it is seen as something we are in together; rather than something developed elsewhere, with Kenya just chosen as a testing site.

IAVI Report: What about concerns by some people that treatments be provided to participants who become infected while in the trial?
Anzala: Participants who get infected while on trial will be given the best possible care we can afford in Kenya. But no matter how much we would like to offer, the budget will only dictate so much. And AIDS treatments are not provided for by the national health care system here.

IAVI Report: Is anybody in Kenya getting AIDS drugs?
Anzala: All the drugs are available here, but only in private patients. And only a very small minority can pay for them.

IAVI Report: Do pregnant women have access to AZT?
Anzala: It is only now that some obstetricians are beginning to talk about this. But I don't know whether the cost of AZT can be reduced enough to make it available across the board.

IAVI Report: How important is it to make the vaccine out of local strains?
Anzala: It's definitely important. Because then it shows that these vaccines are being made with our people in mind and not just for somebody else. So we will test the same vaccine — made from clade A strains – both here and in Oxford. And we've looked for the kind of epitopes that might provide cross-clade protection.

IAVI Report: Some researchers are concerned that people with different HLA types may react differently in terms of generating CTLs. Do you have any feelings on that?
Anzala: That is a concern, so one of the things we've been doing — and this is why our collaboration is so important – is looking at various epitopes that are presented by the different HLA alleles that we see in Kenya. So the epitopes we've picked for these vaccines are the ones that are presented by the common HLA alleles seen here in Kenya.

IAVI Report: So in addition to the HIV subtypes, there may be

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AIDS vaccine as soon as possible but also to make it accessible to anybody in the world who needs it."

Crusaid and the Elton John AIDS Foundation are each donating UK£150,000 toward the vaccine development effort. In addition, IAVI's U.K. partner, the National AIDS Trust (NAT) will contribute UK£80,000 from its recent grant from the Diana, Princess of Wales Memorial Fund to help launch a joint European AIDS vaccine project with IAVI that will be based in London.

U.K.-Kenya Collaboration

A team led by Andrew McMichael, of Oxford University and J.J. Bwayo of the University of Nairobi, will produce an HIV vaccine that combines two separate vaccine constructs: a naked DNA vaccine, plus a modified vaccinia Ankara (MVA) virus vaccine. The work builds on a long standing U.K. Medical Research Council-supported program of work on the immune response to virus infections.

Both vaccines in the Oxford-Nairobi project will be derived from clade A strains of the virus circulating in Kenya. Until now, most AIDS vaccine candidates have been produced from HIV strains prevalent in North America and Europe.

MVA was developed in Germany by Anton Mayr in the 1970s, and the investigators are working with Impfstoffwerk Dessau-Tornau,GmbH, a German pharmaceutical company, to produce the MVA-HIV construct.

U.S.-South African Collaboration

The second partnership, led by Robert Olmsted and Robert Johnston of AlphaVax Human Vaccines Inc., in North Carolina, in collaboration with researchers at the University of Cape Town in South Africa, will develop a vaccine based on Venezuelan Equine Encephalitis (VEE) alphavirus replicon particles. The AlphaVax product will be based on clade C strains from South Africa.

Both product development partnerships were recommended for funding by IAVI's Scientific Advisory Committee (SAC), which selected them after reviewing a range of proposals from around the world.

"These are two of the most promising new vaccine technologies in the world," said Jaap Goudsmit of the University of Amsterdam, who also chairs IAVI's SAC. "They are also far enough along in the development process that we should be able to test them quickly in humans," he added.

Investment Includes Unique Intellectual Property Rights

In launching its first two vaccine development partnerships, IAVI has secured unique intellectual property (IP) and technology-transfer agreements that will help make a successful vaccine available in developing countries at a reasonable price. In return, IAVI's investment will enhance the value of its partners' intellectual property, without interfering in their most profitable markets.

"We are combining the best mechanisms of the for-profit and not-for-profit sectors to achieve our goals," says Lita Nelsen, director of the technology licensing office of the Massachusetts Institute of Technology, who served as IAVI's principal adviser on intellectual property issues.

For-profit companies are where most of the world's vaccine development expertise resides. IAVI and its partners have sought to create a "win-win" situation to fully engage the expertise of the private sector, ensure that development moves ahead rapidly and that access issues are addressed early on.

"The current paradigm, where vaccines are developed in the industrialized world and sold exclusively for 10 to 15 years at high prices to recoup R & D costs, should not be acceptable for any vaccine, and certainly not for AIDS." added IAVI's Seth Berkley. "Our goal is to simultaneously launch a successful HIV vaccine in the North and South."

In the broadest sense, intellectual property is the intangible property based on creations of the mind. Mechanisms such as patents, copyrights and trademarks all provide legal ownership and protection for these rights. Licensing of intellectual property allows a party to use such rights without obtaining ownership.

IAVI's investment in the two product development teams is unique in that it enables the Initiative to help make intellectual property rights generated by the research available to the public sector of developing countries. The agreements require both parties to make their best efforts to provide vaccines produced from the collaboration to developing countries at reasonable prices. These prices are based upon the total production costs incurred. To lower costs, IAVI has the right to bring in third party contractors to bid on producing the vaccine.

In both agreements, IAVI also has specific IP rights to produce the vaccine for developing countries under certain conditions. In addition, the Initiative could receive royalties on industrial country sales of products generated by research.

IAVI decided early on that, when funding research and development, it would seek to protect the IP generated from such research. The Initiative is committed to using these rights to ensure access rather than profit. In August 1996, IAVI invited key authorities on intellectual property (from the fields of law, biotechnology, public health and academia) to discuss how these issues would impact AIDS vaccine development (available at IAVI's website: www.iavi.org).

Other leading researchers also expressed excitement about the approaches. Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), told *Science* magazine that "both of the IAVI vaccine initiatives hold promise." He added that NIAID might provide additional support should one or both of the approaches show favorable results in humans.

IAVI's scientific strategy is to ensure that every promising vaccine design is pursued as quickly as possible. That strategy - of moving multiple vaccine candidates forward in partnership with vaccine producers and developing countries - was outlined in the Initiative's *Scientific Blueprint for AIDS Vaccine Development*, released last June at the 12th World AIDS Conference.

Minister Short noted that "As the first Government partner of IAVI, the U.K. is taking a lead to ensure finance for vaccine development within G8 countries, the World Bank, and the international community. To make a vaccine widely available, I am keen to help establish and finance the necessary international mechanisms."

Tests in Humans Could Begin This Year

"IAVI's support," according to McMichael, "will enable us to collaborate with Dr. Bwayo's team and take our vaccine candidate to Kenya after initial testing in the U.K. We hope to begin Phase I trials in Oxford next year and in Kenya by 2000.

AlphaVax's Johnston noted that "we have been working for approximately ten years on the scientific underpinnings of this technology and, for the last five years, on its application to an HIV vaccine. We are delighted to work with IAVI and our South African colleagues to design an HIV vaccine for Southern Africa and move it into clinical trials."

"The HIV epidemic poses the single greatest threat to the African Renaissance," said William Makgoba, president of South Africa's Medical Research Council," The MRC will work with IAVI and AlphaVax in the development of suitable and specific vaccines for our people." ◆

A Closer Look at the Two Vaccine Approaches

DNA plus MVA (U.K.-Kenya)

Andrew McMichael's Oxford University team has developed a unique and promising approach in which two different vaccine constructs are designed to act in synergy: 1) an HIV DNA vaccine; and 2) a safe vaccinia virus (modified vaccinia Ankara, MVA) engineered to express HIV core proteins. An immunologist, McMichael has pioneered state-of-the-art methods to measure immune responses in animals and humans.

DNA vaccines (also known as "naked" DNA vaccines) consist of bacterial plasmids with genetic material of a pathogen (such as HIV) inserted in the plasmid. When the purified plasmid is injected directly into a human or an animal, the DNA is taken up into cells, and the vaccine proteins encoded by the DNA are expressed in those cells. These expressed proteins generate immune response in the vaccine recipient that will hopefully provide protection.

MVA is a vaccinia virus that has been attenuated by multiple passages in chicken embryos. It has a strong safety profile, having been used as a smallpox vaccine in more than 120,000 people without significant side effects. MVA does not replicate in human and most other mammalian cells and, unlike vaccinia, appears to be non-pathogenic in immune-suppressed animals. The vector has a large capacity for inserted genetic material, which allows for high levels of expression. Both the DNA and MVA constructs contain multiple core protein epitopes from SIV and HIV proteins. A team at Oxford is also studying this DNA/MVA combination as a vaccine for malaria.

Studies by the Oxford researchers demonstrate that the DNA/MVA combination generates strong, durable T cell responses (both T-helper and CTL) in both mice and monkeys. Early studies in mice have enabled the research team to improve the approach to generate stronger immune responses.

VEE Replicons (U.S.-South Africa)

AlphaVax researchers have constructed an alphavirus "replicon" vaccine for SIV that has yielded extremely promising data in a pilot study in monkeys. Early results indicate that several vaccinated monkeys show some evidence of protection against clinical disease following high dose intravenous challenge with a pathogenic SIV strain. Other than live attenuated SIV vaccines, this level of protection, using a virus vector approach by itself, has not been previously demonstrated in the SIV/monkey model.

The technology, developed by researchers at the University of North Carolina and the Army Medical Research Institute of Infectious Diseases (USAMRIID), is derived from an attenuated form of Venezuelan equine encephalitis (VEE) virus, which has been modified to enhance its delivery properties and eliminate its disease-causing properties. One-third of the virus' genetic material has been removed and in its place SIV *gag* or gp160 have been inserted. The vector has been engineered to generate VEE replicon particles (known as VRPs) that can infect cells but not replicate beyond the initial site of infection. The VRP approach has demonstrated a high margin of safety in all rodents and monkeys inoculated to date.

The advantages of the VRP approach are: 1) it provides high levels of expression of the antigen; 2) it targets lymphoid tissues; and 3) it induces both humoral and cellular immune responses.

To follow up the encouraging initial results, AlphaVax is modifying the SIV-VRP vaccine to further improve its immunogenicity and efficacy. These improvements will be incorporated into the candidate HIV vaccine, HIV-VRP. In a separate experiment, researchers at USAMRIID researchers recently reported that a VRP vaccine protected monkeys against Marburg virus, an extremely deadly pathogen related to the Ebola virus. ◆

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are protection experiments with WK virus from a mutant SIV strain (developed in Ronald Desrosier's lab at Harvard) that shows decreased glycosylation of the envelope protein and induces stronger antibody responses in infected monkeys.

If these proof-of-concept studies pan out, many other tasks lie ahead, say Arthur and Lifson. One is to try to develop a second inactivation step, such as a physical agent, or to switch to a non-infectious (mutant) HIV strain, both of which would increase the candidate vaccine's safety profile. Another is to test the WK particles in a prime boost combination with an immunogen (such as a DNA vaccine) that presents HIV antigens to the immune system as a complex with host cell surface molecules – the "classical" way to elicit cellular immunity.

"My sense is that the safety problems can ultimately be addressed."
– Karen Goldenthal, U.S. FDA

Another promising approach is emerging from a collaboration between Irvin Chen at the UCLA School of Medicine and Dorman and Joyfau Hsu at Acrogen. By systematically testing various combinations of heat and formalin (two classical ways to inactivate virus) and different purification procedures, they devised a simple protocol for killing HIV without apparently destroying its immunogenicity, as shown by retention of three specific epitopes on the gp120 envelope. Although the method does not work on all strains – some, particularly lab-adapted ones, still shed their envelope – it works well on others, including some primary isolates, says Chen.

As they worked out the procedure, the researchers detected a notable change: an increase of roughly 5-fold in the level of one of the three epitopes they followed, as measured by antibody binding assays on WK versus untreated virions. That could be a crucial finding, since this particular epitope is normally expressed at enhanced levels only fleetingly while HIV fuses with the CD4 receptor on the surface of the cell it is infecting. And this increase could be significant, since such transient, so-called "fusion epitopes" were recently shown by Jack Nunberg's team at the University of Montana to elicit antibodies in mice that neutralize a wide range of primary HIV isolates – a striking result not seen with any other envelope antigens.

Testing these WK-HIV particles in animals is now a top priority, says Chen, beginning with immunogenicity studies in mice. But the experiments he would most like to do – infecting monkeys with WK particles of SHIV, a virus with an HIV envelope and SIV core proteins, and testing for immunogenicity and ability to protect against disease – is beyond reach for now, since the researchers have neither the access to a primate facility nor the funds for such work.

For the past eight years, a small group in John Oxford's lab at the London Hospital Medical College has also been working on WK-HIV, in a partnership with Retroscreen, Inc., the hospital's commercial arm, and the Istituto Superiore di Sanita (ISI) in Rome. The researchers use two inactivating agents (beta-propiolactone and binary ethylenimine) that together achieve a theoretical killing of roughly 20 logs, which provides a wide safety margin. They have also worked out methods for growing and inactivating batches of HIV using the lab-adapted MN strain (clade B) and are extending this to other clades.

Based on immune responses seen in small animals, Oxford says that his inactivation procedure seems to preserve the virions' immunogenicity. The animals show a strong antibody response, primarily to spike protein and p24 *gag*, but comparatively weak cellular responses. However, while antibodies to MN neutralize other clade B strains, they do not cross-neutralize other clades. If the same limitation holds for WK vaccines made with clade C and E virions, Oxford will try the flu vaccine "cocktail" strategy.

Moving into primates, a first attempt to evaluate their WK vaccine design in monkeys proved disappointing: inactivated SIV turned out to be poorly immunogenic in monkeys, suggesting that it is over-inactivated. Not surprisingly, recent sutdies by P. Verani and F. Titti in Rome showed that it also failed to protect the animals from a live SIV challenge. So the plan is now to try SHIV by testing whether it can be inactivated without sacrificing immunogenicity; if so, it would provide an alternative for protection experiments.

In parallel to the animal studies, scientists at a GLP/GMP lab should soon begin working on scaling up production of Oxford's WK-HIV vaccine candidate to standards of the Medicines Control Agency (MCA), Britain's medical licensing agency, for testing in humans. If they achieve that, says Oxford, the next aim will be a Phase I trial in HIV-infected individuals, to test whether the vaccine is immunogenic in humans – an approach he discussed with MCA officials during a November, 1998 meeting and which got an "encouraging" reaction. The officials also said that primate protection data should not be required for such a trial.

While the Arthur and Oxford teams have taken great pains to keep HIV particles fully intact, Immune Response Corporation (IRC) – a small California-based company and the veteran of the WK-HIV field – has taken a different path: its inactivated virions lack gp120, but retain the more conserved gp41. Developed as a therapeutic vaccine called Remune®, this WK-HIV immunogen has been extensively tested in HIV-positive people, and the company is now examining whether it has potential as a preventive vaccine.

The project dates back to 1986 when Jonas Salk developed the idea of immunizing HIV-infected people to boost their cellular immune responses, which he considered the key to controlling AIDS. After inactivating a Zairian clade A/G recombinant strain with beta-propiolactone followed by gamma irradiation and then purifying the virus, the resulting particles turned out to have lost all detectable gp120. Against the prevailing view that envelope antigens might be important for protection, IRC stayed with its gp120-depleted virions, based on the rationale that high levels of gp120 antibodies do not correlate with better clinical outcomes in infected people–and therefore may not be crucial. More recent work has strengthened this view, says IRC's Ronald Moss, especially the findings of research teams led by Bruce Walker and Andrew McMichael that reduced viral load in HIV-positive nonprogressors correlates most strongly with cellular responses (CD4+ T-helper cells) to the p24 *gag* protein, not to envelope.

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Earlier human trials showed that Remune stimulates immune responses to all HIV proteins except gp120. Now, studies of its clinical efficacy, when used with anti-viral drugs, are underway in a Phase III trial involving 2500 HIV-positive people. One small (43 person) trial of the combination treatment, presented at the June, 1998 AIDS meeting in Geneva, showed that it induces strong lymphoproliferative responses to the immunogen, to p24 protein and to virus of another clade (B), along with enhanced production of beta-chemokines – the same responses as those seen in nonprogressors, says Moss.

These findings have prompted IRC, together with Peter Salk (Jonas' son) at the Jonas Salk Foundation, to look at using Remune as a preventive vaccine. The first experiments compared different doses, schedules and adjuvants in mice to find the best protocol for inducing cellular responses, which turned out to involve low-dose immunization. IRC recently teamed up with researchers from the Walter Reed Army Institute for Research and NIAID to initiate similar studies in 22 macaques.

If the animals show strong cellular immune (cytokine and proliferative) responses, the next step will probably be protection experiments, says Salk. But those might prove ambiguous: a negative result could reflect either a real failure of the vaccine or simply an insufficient cross-reaction between the (HIV) immunogen and the (SIV) challenge, an issue the researchers have begun to examine. Chimps are a potential alternative to monkeys, albeit an expensive one – but funds for this research are scarce. And liability for eventual trials in HIV-negative people remains a huge, unresolved issue for the future.

A new group poised to enter the WK-HIV field is the Aphios Corporation in Woburn, MA, which brings with it a novel method for inactivating viruses. By infiltrating virions with highly compressed liquids called "superfluids" and then decompressing them, the virions rupture at their weakest point but otherwise remain intact. Soon to go commercial as a method for killing viruses in blood plasma, the procedure, according to Aphios CEO Trevor Castor, is fast, cheap and easy to scale up. The company will start working on a therapeutic HIV vaccine, and possibly extend into preventive ones later on.

The Outlook for Whole Killed HIV Vaccines

Even if research shows any of these WK candidates to hold promise, moving it into human trials will require tackling tough safety, manufacturing and regulatory issues. Some of the groundwork for this was laid at a workshop on the potential risks of WK-HIV vaccines, held at the 1996 meeting of the National Cooperative Vaccine Development Group for AIDS in Bethesda. One concern is the need to grow virus in established cell lines, which has been avoided with other preventive vaccines since it could theoretically transmit harmful agents, such as viruses, cellular oncogenes or other segments of DNA to vaccinees. Another potential risk is incomplete virus inactivation. Although the workshop did not resolve all the issues, "my sense is that the safety problems can ultimately be addressed," says the FDA's Karen Goldenthal, Director of the Division of Vaccine Applications, one of the participants.

Some hints as to how that might work come from IRC's experience getting FDA approval for the Remune trials (though WK-HIV trials in uninfected people could well require additional precautions). Use of a T-cell line for virus production was not an obstacle, says Moss, since IRC showed that inactivation effectively destroys all nucleic acids (including those from the host cells), while the cell line has been extensively characterized with respect to endogenous viruses and other potential dangers. The bigger problem (eventually overcome) was growing enough virus to show the amount of killing the FDA wanted to see, which went far beyond any theoretical risks; IRC now has a GMP-grade manufacturing plant that can make up to a million doses of Remune per year. And, there is now data on more than 4000 people who have received Remune, some followed for 6 or more years (a few up to 11), and no adverse effects or safety problems have emerged, says Moss.

Moving promising WK-HIV vaccines forward will also mean optimizing virus production for the lowest possible cost; at present, growing and purifying HIV to a high standard is relatively expensive. That task, in turn, may depend on funding–which could get a boost through NIAID's new plan to provide substantial, long-term support for vaccine design and development teams.

That would be a great boon to the field, say advocates of the WK approach. "One of the main arguments for a WK strategy," says Acrogen's Dorman, "is that it uses 'off-the-shelf' technology, so a candidate WK-HIV vaccine could probably be readied for testing sooner than most other types of vaccines under development. And whole inactivated approaches have succeeded for some viruses related to HIV. Given that it takes relatively little to see if this works, it seems a real tragedy to spend more years overlooking such an obvious opportunity." ◆

VACCINE BRIEFS

UK MP's Support AIDS Vaccines, IAVI

A total of 46 Members of Parliament have endorsed a resolution congratulating the U.K. government for being the first to contribute financially to IAVI. The resolution notes that although 30 million people are infected with HIV around the world, only one percent of all AIDS spending is devoted to AIDS vaccine development. It called on all Western governments to contribute to research "so that AIDS can be controlled for the next generation."

Wayne Koff, Others Join IAVI

Wayne Koff has been appointed IAVI's Vice President for Research and Development. Koff was Senior VP for corporate development and vaccines at United Biomedical Inc (UBI), of Happaugue, New York. From 1988 to 1992, he led the NIH's AIDS vaccine research effort as branch chief for vaccine R & D at NIAID's Division of AIDS.

At UBI, Koff oversaw the company's HIV vaccine development program and successfully launched the first HIV vaccine trials in Thailand, China and Brasil. "We are extremely excited that Wayne is joining IAVI," said Seth Berkley. "He is an outstanding researcher whose commitment to developing safe and effective AIDS vaccines is well-known. He brings a wealth of government, industry and, most critically, international AIDS vaccine development experience to IAVI."

In addition to the appointment of Patricia Kahn as associate editor of the *IAVI Report* (see page 9), the Initiative also announced the appointments of Nick Marinacci as director of finance and administration and Cliff Lenton as Director of IAVI-Europe. Marinacci had previously served as regional director for Save the Children in the Caucasus and also worked with the International Rescue Committee in Bosnia and Hercegovina. Lenton had previously worked as Director of Resource Development for International Planned Parenthood Federation in London and as a Health and Population Officer for the U.K. Overseas Development Administration.

NIH Reportedly Close to Hiring Vaccine Center Head

As the *IAVI Report* went to press, informed sources report that the U.S. NIH is very close to appointing Gary Nable, a researcher at the University of Michigan's Howard Hughes Medical Center, to be director of its Vaccine Research Center. Establishment of the vaccine center was first announced by U.S. President Bill Clinton in May 1997. Vaccine advocates have grown frustrated at the NIH's long search for a leader of the center. NIH had been reportedly looking for an individual with experience in producing vaccines and a private sector background. Nable's research appears to be primarily focused on gene therapy. However, he is well-respected scientist, and, according to Brenda Lein of the U.S. advocacy group Project Inform, is "bright, well-motivated and easy to work with." Lein, who has worked with Nable on the group's immune restoration project, also notes that the Michigan researcher has experience in taking new gene-based technology into the clinic without pharmaceutical backing.

Indian Government Supports AIDS Vaccines

India is creating a national AIDS vaccine development program. At the 10th International Congress on Immunology in New Delhi in November, Indian and non-Indian scientists discussed the involvement of the country's scientists and facilities in AIDS vaccine research. IAVI's Seth Berkley attended the meeting and discussed the Initiative's potential participation in the program. India has agreed to launch an effort to conduct trials of AIDS vaccines developed domestically or by an international team of researchers. Indian officials hope to develop a low-cost vaccine based on virus isolates from India.

Paul Corser (1961-1999)

Paul Corser, senior program officer for the American Foundation for AIDS Research (AmFAR), died of AIDS-related complications on 3 January 1999. Corser played a major role in AmFar's AIDS vaccine efforts, overseeing its research grants in the area of vaccines, the launch of the HIV Vaccine Directory as part of the organization's well-established AIDS/HIV Treatment Directory and its critical early support for the AIDS Vaccine Advocacy Coalition. Corser also had a significant impact on many other AmFAR initiatives, including creating the Community-based Clinical Trials Network and overseeing funding and advocacy of needle exchange programs. On a personal level, Paul was an extremely effective, pragmatic and generous person. He scrupulously avoided the personal battles and rivalries that those working in AIDS often become involved in. Paul leaves a legacy of long-lasting accomplishments, unparalleled integrity and a wonderful sense of humor. Our deepest sympathies to his family, friends, and co-workers and most especially to his loving wife, Sally Morrison.

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is not NIH's central mission. The goal is for companies and academic researchers to collaborate on product development with resources from NIH.

IAVI Report: Did you know that the U.S. Army Walter Reed program was just cut?
Nathanson: Looking at what the President says, and how small a part of the defense budget this is, I can't believe that anybody would consciously cut a vaccine development program. One of the mandates we have is to encourage communication among the elements of the federal government, the Army, CDC, NIH and USAID. We're all in this together, and it's important to support all programs.

Europe has many dedicated, very high quality AIDS researchers and they complain bitterly about being under-funded.

IAVI Report: How much of the NIH vaccine budget goes to extramural versus intramural research?
Nathanson: Probably no more than US$25 million is intramural. The general rule of thumb for NIH is that nine of every ten dollars is spent extramurally. The intramural vaccine program is designed in the classic biomedical tradition of letting researchers do what they find most interesting.

IAVI Report: Are you satisfied with the quality of the extramural research?
Nathanson: The program supports a lot of high-quality research. There's very little published on AIDS vaccines that isn't at least partially supported by the NIH. Undoubtedly, some researchers are not as productive, and some projects aren't as good. But, frankly, the urgency is such that I would accept a certain amount of risk-taking to ensure that every project with potential is funded. You can't have cost efficiency and maximum speed, at the same time. So speed and urgency take precedence.

IAVI Report: Your predecessor, Bill Paul, had some conflicts with key NIH institute heads, leading some people to believe that the position is a tough one. Do you have any sense of that?
Nathanson: Yes, I do. And it's a delicate matter, so I won't say too much about it. But what I have tried to do is carve out a role for our office that is complementary to what the institutes do, not competing with them. So when people ask us to deal with a perceived problem — we usually refer these to the institutes, because it falls within their jurisdiction, not ours. I've been quite firm about that. We try to provide an overarching vision, set of priorities and coordination for AIDS programs across all of NIH.

IAVI Report: You have a certain amount of discretionary funds at your disposal.
Nathanson: Yes, but they represent one percent of the budget and should really be used as contingencies, not for major, new initiatives.

IAVI Report: You've been on the job since July. Anything that's particularly surprised you?
Nathanson: Not really. Though it's somewhat different viewing the office from the inside. If anything has been a surprise, it's been that, in addition to program coordination and prioritization, we have a major role in public liaison, and that means dealing with advocate groups, Congress, the White House and the Department of Health and Human Services.

What bemuses me are the crises created around a media event, where we essentially have to drop everything, and provide a press release, on 24 hours notice. Then we go back to doing what we should be doing. But that's part of our job. AIDS can still be a politically charged situation.

IAVI Report: The bully pulpit role may be one of the most important roles of the OAR director.
Nathanson: Right. Some media reports have suggested that AIDS is over-funded relative to other diseases. So one of our roles is to justify the prioritization of AIDS. And I embrace that with enthusiasm, because the public may not understand what makes AIDS different. Major diseases — like cancer and heart disease, the ones often invoked — are not infectious, transmissible diseases. AIDS has gone from nothing to the plague of the twentieth century in fifteen years. That would be unthinkable with a non-transmissible disease.

And the possibility of intervening with effective therapies and a vaccine, thereby putting the epidemic under control in a short time, is something you just can't do with cancer or heart disease. So there's justification for a very intensive effort.

IAVI Report: Are you optimistic about prospects for a vaccine?
Nathanson: I am fairly optimistic that we will find something, within what is already identified, that will be at least partially protective. And eventually, we'll find something that is far more effective. The problem is there is still an enormously long time period between moving a promising idea into human trials.

IAVI Report: Do you see any competition for resources within the AIDS research budget among treatments, vaccines or non-vaccine prevention?
Nathanson: Luckily, we have the luxury of enough resources so there is no reason for competition. Some people may be concerned that treatments have been put aside with the new prevention initiatives. I don't see that. This office is committed to ensuring that NIH sufficiently supports research on developing more effective and safer HIV treatments.

IAVI Report: Within the prevention arena, how do you decide how much is spent on condom, microbicide or vaccine research?
Nathanson: It's somewhat of a judgment call, depending on

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NATHANSON INTERVIEW
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what needs to be done and the size of the research community. Our vaccine effort seeks to ensure that everybody who might contribute has money for their research. But microbicide research is important and we've made very little progress in this area.

IAVI Report: Do you think the other wealthy industrialized countries are making a sufficient investment in AIDS vaccine research?
Nathanson: Absolutely not. Look at the investment in AIDS research in Europe, which roughly has the same resources as the U.S. Granted, they have more economic problems, but compared to our US$1.9 billion, Europe is spending much less. It may not be a popular thing to say, but at a government level, I think they have been quite derelict. Europe has many dedicated, very high-quality researchers and they complain bitterly about being under-funded.

IAVI Report: Are ethical concerns going to be a significant problem in conducting efficacy trials?
Nathanson: It's a problem, but one that can be dealt with. Fortunately, there's a healthy, open debate and the basic conclusion seems to be that the host country and developed country should negotiate so both parties get reasonable benefits from the trials.

When I was in Africa, people said "don't exclude us in your too-holy desire to make sure everything is ethical. Let us decide what is acceptable." They don't want their country excluded from research because an ethicist, sitting three thousand miles away, made some judgment.

IAVI Report: Have we gotten past the debate between empiricists and basic research advocates in vaccine development?
Nathanson: I hope so. Most vaccines have been developed partly in an empirical way without a total biological understanding. We made these vaccines, they worked, and we really didn't understand all the science. So, certainly, a lot of vaccinology is trial and error.

IAVI Report: You provided some advice to IAVI on its product development team awards.
Nathanson: I was very impressed by the quality of the scientific advisory committee, and the dialogue. The two projects that were funded are excellent projects with outstanding investigators. Does this imply that there's something wrong with the NIH? Absolutely not. There is a long-standing tradition of not-for-profit, private outfits like the American Heart Association, the American Cancer Society that have made major contributions. They can do things that the NIH can't do.

IAVI Report: Two years from now, how do we judge whether you've been successful in moving the vaccine effort forward?
Nathanson: I'll leave that to other people. Since an AIDS vaccine is going to be a slow process, you may need the hindsight of thirty years, rather than two years. All I can say is that we are attempting to play a catalytic role in identifying the gaps in the vaccine development program and take steps to overcome them. ◆

WHOLE KILLED VACCINES FOR ANIMAL RETROVIRUSES
continued from page 4

across many strains. A live attenuated vaccine developed in China also seems to be effective in horses, while a subunit vaccine causes severe enhancement of disease, says Montelaro.

EIAV is somewhat different from HIV in its genome and its biology. A few weeks after becoming infected, horses suffer a severe bout of anemia and wasting, from which they usually recover quickly. Several weeks later the illness returns and the animal generally recovers again–and so it continues for up to a year as virus and host fight a long, drawn-out immunological battle, with the horse usually winning in the end once it finally establishes an enduring protection.

Whether by natural infection or vaccination, reaching this state of full protection appears to involve a complex evolution of both humoral and cellular responses. Neutralizing antibodies are not necessary, while "very good protection occurs without an overwhelming amount of CTLs," says Montelaro, who is analyzing the changes taking place. His goal: to find out why it takes so long for the immune system to get it right–and just what "it" is in the end. ◆

ANZALA INTERVIEW
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other scientific reasons for making a vaccine specifically produced for Kenya?
Anzala: Exactly. For example, we know that the HLA B57 allele is very common in Kenya. So we will look for the HIV epitopes presented by B57 and make sure that they are presented in the vaccine.

IAVI Report: What do you think the biggest hurdle is to testing vaccines in Kenya?
Anzala: Our biggest step will be getting ethical approval. We have been working to get the political establishment to realize that this is an important undertaking, so that they can really support it.

IAVI Report: Are you optimistic that an AIDS vaccine is going to be developed?
Anzala: I think so. We believe that the information we've learned about the role of CTLs is important. Our vaccine is designed to elicit that kind of immune response. Even if it doesn't work, we are going to learn a lot in the process. And this information will go a long way in helping us modify the vaccine and eventually making it work.

IAVI Report: Can you tell us about your background and how you got involved in this?
Anzala: I was trained as a physician here and worked as a research assistant in the Medical Microbiology Department at the University of Nairobi. I then got a scholarship to study virology and immunology in Canada. And on completing my Ph.D., I joined Oxford University because they are well known for immunology and have continued my research in HIV with a joint appointment at Oxford and the University of Nairobi. ◆

Letter to the Editor

To the Editor:

The error in a letter to the editor in the last issue prompts this response. Stephen Johnston's complaint about your article interviewing me (*IAVI Report*, vol.3, no.3) was invalid. He complained that we didn't reference his paper, but we had, and we had even described his results in the text of our *Science* paper.

Our results were obviously quite different from what he had published, or *Science* would not have published our paper and highlighted it with a commentary by Jon Cohen. The technology is different, and the results were dramatically different since we: 1) utilized "naked" DNA; 2) used an antigen from a pathogen; 3) demonstrated both humoral AND cellular immunity (the latter being the biggest challenge); and 4) demonstrated protection from viral challenge. Scientists and laymen alike called our *Science* results "startling" (or more pejoratively "weird" or "cold fusion" because they were so surprising).

Regarding naming the technology, "a rose is a rose is a rose, except when its not a rose." Two international gatherings of scientists involved in DNA vaccines voted against the name "genetic vaccination" since that term implies chromosomal integration, which is not thought to occur with DNA vaccine or with RNA gene-based vaccines such as replicons.

IAVI is to be commended for focusing attention where it belongs: on how to most aggressively advance efforts to make a vaccine to prevent and treat AIDS. It is much too early to worry about who gets credit since so much work lies ahead. Let's direct our efforts to conquering AIDS.

Margaret A. Liu, M.D.
Vice President
Vaccines and Gene Therapy Research
Chiron Corporation

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vector, DNA) all expressing the same SIV *gag* and SHIV 89.6 *env* antigen. The vaccine concepts would be tested in combinations with each other and with a clade B HIV gp120. All animals would be evaluated for immune responses and viral load. The Council stressed that this study would be very useful but should not be a "gatekeeper" for concepts to enter human trials, since the predictiveness of primate models is still unknown.

NIH Readiness To Support International Vaccine Trials

The OAR Council heard presentations about the reorganization and new competition for a new NIH-sponsored Vaccine Trials Network (VTN) to conduct clinical trials of HIV vaccines, and a new Prevention Trials Network (PTN) focused on clinical evaluation of microbicides, perinatal treatments, behavioral interventions and other prevention research. The first round of applications, due in February 1999, will be for "leadership groups" for the VTN and PTN, and will include the statistical centers, core laboratories, and coordinating research teams. The second Request for Applications will call for individual sites to apply by August 1999 to be a part of the VTN or PTN. International research sites are encouraged to apply. Sites may be part of both the VTN and PTN, and may apply within the leadership group and also as individual sites.

NIAID officials assured the OAR Council that NIH was committed to Phase III trials in 2000 and beyond, and to a truly international effort. They discussed efforts to collaborate with VaxGen on its. Phase III gp 120 trial in the U.S. Representatives from a number of organizations, including IAVI, spoke of the importance of international HIV vaccine trials. The Council called on the OAR and the NIH to increase collaboration with U.S. and international organizations.

Sam Avrett is executive director of the Washington, D.C.-based AIDS Vaccine Advocacy Coalition

IAVI REPORT

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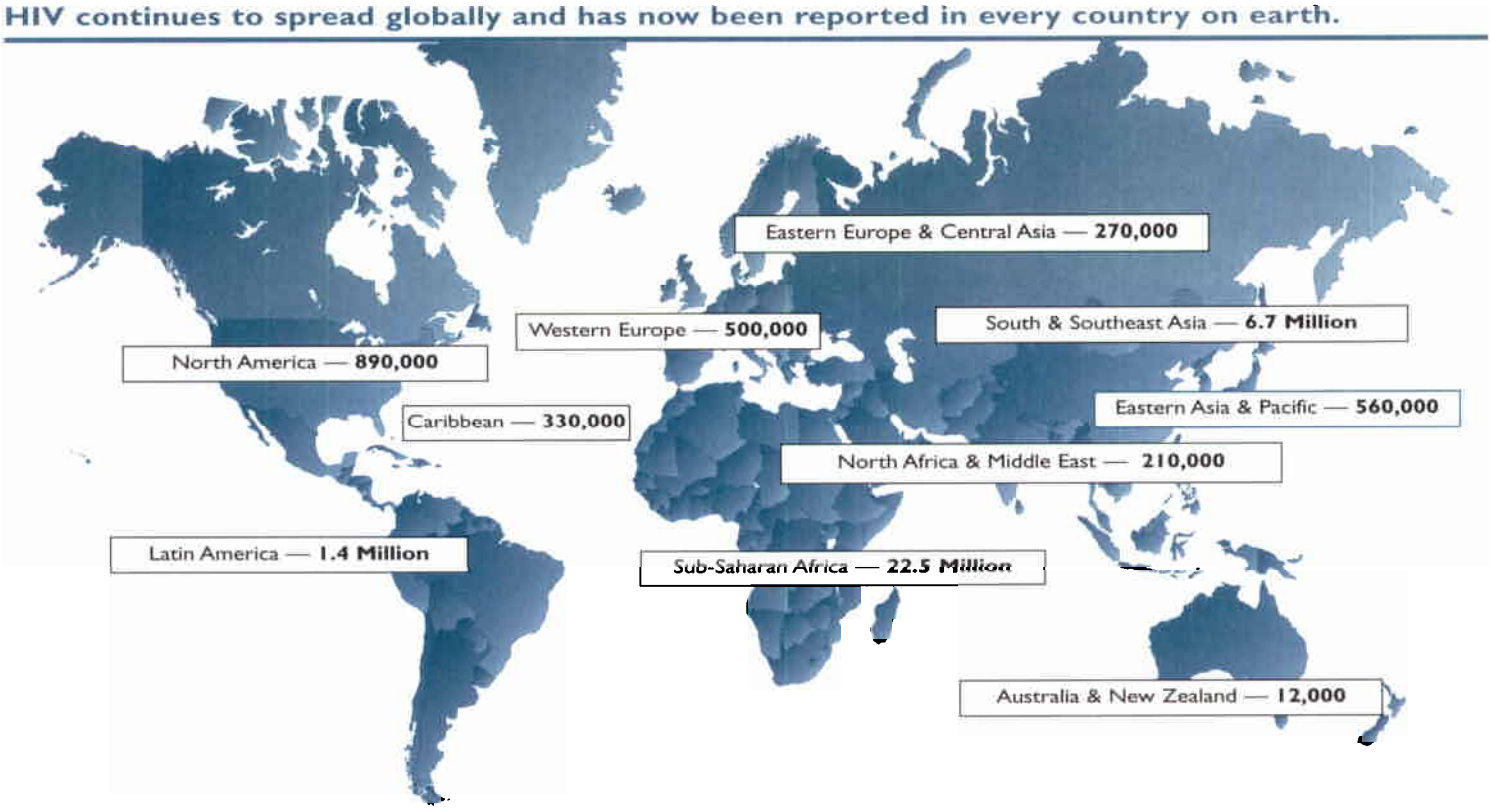
IAVI is a scientific organisation founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Lean in structure and catalytic in nature, IAVI focuses on three key areas: accelerating scientific progress; education and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

IAVI is a UNAIDS Collaborating Centre. Its supporters include the Rockefeller, Alfred P. Sloan, Starr, William H. Gates, Until There's A Cure and the Vincent P. Belotsky, Jr. Foundations, as well as the World Bank, UNAIDS, the National AIDS Trust and Fondation Marcel Mérieux. IAVI also receives support from the UK Government, Crusaid, the Elton John AIDS Foundation, Levi Strauss International, Angel Music, Ltd., Glaxo Wellcome and generous individuals around the world.

The Global AIDS Epidemic: No Place on Earth Untouched

According to estimates by the Joint United Nations Programme on AIDS (UNAIDS), HIV continues to spread globally and has now been reported in every country on earth.



Global Summary of the HIV/AIDS Epidemic

People living with HIV	33.4 million
People newly infected with HIV in 1998	5.8 million
AIDS deaths in 1998	2.5 million
People infected with HIV since beginning of epidemic	47.3 million
Total AIDS deaths since beginning of epidemic	13.9 million

Source: UNAIDS; December 1998

The Epidemic in Young People

- ☞ **600,000 children below age 15 were infected with HIV in 1998**
- ☞ **500,000 children below age 15 died from aIDS in 1998**
- ☞ **7,000 people aged 10-24 are infected with HIV every day**
- ☞ 1.7 million young people in Africa are infected every day
- ☞ 700,000 in Asia and the Pacific are infected every day

AIDS Facts

- **Total number of people dying of AIDS by year 2000, 1994 prediction: 8 million; total number of lives taken by AIDS already: 13.9 million**
- **Reduction in years of life expectancy due to AIDS in Botswana: 20**
- **Estimated increase in current national health budget in South Africa required to treat all AIDS cases in year 2000: 10-fold**
- **In the four worst affected countries in sub-Sahara Africa, between 20-26% of people aged 15-49 are infected with HIV**
- **People newly infected with HIV in the U.S. in 1998: 60,000**

For more information, visit: www.iavi.org or www.unaids.org