# IAVI REPORT

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INTERNATIONAL AIDS VACCINE INITIATIVE

# Using Recombinant Vectors as HIV Vaccines

*A wide range of vectors are being studied, but so far only a few have moved into human studies*

*by Alan Schultz, Ph.D.*

Vector-based HIV vaccines consist of harmless viruses or bacteria into which HIV genes have been genetically (recombinantly) inserted. When an individual is immunized with a vector-based (or "live vector") HIV vaccine, HIV proteins or peptides are produced in the body by the vector as it replicates. This will, hopefully, elicit immune responses that can protect those who receive the vaccine if they are subsequently exposed to HIV.

Researchers around the world are studying a wide range of recombinant vectors for use in HIV vaccines. Only a relatively small number of these, however, have moved into human studies. Yet one of the recombinant vector vaccines (Pasteur-Mérieux-Connaught's canarypox construct, given with a gp120 boost) is among the approaches most likely to reach Phase III efficacy studies by the end of the decade.

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## Vaccines High on the Agenda at AIDS in Africa Meeting

More than 5,000 researchers, healthcare professionals and activists gathered in Abidjan, the capital of the Ivory Coast, for the 10th International Conference on Sexually Transmitted Diseases and AIDS on 7-11 December 1997. The need for a more aggressive and well-funded HIV vaccine research effort was a key topic of discussion at the meeting.

Speaking at the opening ceremonies, French President Jacques Chirac called for massive new efforts to bring better treatments and a preventative vaccine to developing countries. President Chirac stressed that an HIV vaccine was the only way to eradicate the disease in many parts of the world, including Africa. According to new UNAIDS estimates, more than two-thirds of the world's 30.6 million HIV-infected people live in Africa.

"I realize how difficult it is to develop a vaccine, but this is a goal of such overwhelming importance that everything must be done to achieve it," the French President said. He stressed that France would do whatever was required to secure the support of its European partners in promoting access to treatment and funding for vaccine research. President Chirac also promised to push hard for concrete action at the next meeting of the G-8

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### Starr Foundation Becomes IAVI Founding Partner

As the *IAVI Report* goes to press, we have learned that the Starr Foundation has joined the Rockefeller and Sloan Foundations as Founding Partners of IAVI. In doing so, the Foundation, which is based in New York City, is providing IAVI with an unrestricted grant of US$4 million over three years. We will provide further information on the Starr Foundation and its commitment to advancing the global HIV vaccine effort in our next issue.

## Background

A child who recovers from the basic childhood infections (such as mumps, measles or chickenpox) will usually have lifelong immunity to these infections. In a similar way, many licensed vaccines in use today depend on infection with weakened or attenuated strains of a pathogen to induce long-lasting resistance to the pathogen. Immunization with these live vaccines efficiently generates protective immunity.

With the tools of contemporary genetic engineering, viruses or bacteria can be modified to incorporate passenger genes. These viruses or bacteria then become live vectors (or "carriers") which "express" the foreign passenger genes as well as their own genes upon immunization. If the immunized individual makes good immune responses to the proteins or peptides encoded in the vector, that person will hopefully become immune to the virus that the foreign passenger genes came from.

*The promise of vectored vaccines is that they may strike a balance between the immunogenicity of live attenuated vaccines and the safety of subunit constructs.*

This theory is the basis for development of recombinant vectored vaccines. The concept is especially attractive in developing HIV vaccines, since the traditional approaches of attenuated and whole killed vaccines could entail some risk to those who are immunized.

Therefore, for safety reasons, it is preferable to induce effective immunity to HIV by exposing the vaccine recipient to pieces of HIV instead of the whole virus, if possible. However, for most diseases, infection with a live attenuated vaccine induces more potent immunity than immunization with "dead" proteins or virus subunits. The promise of vectored vaccines is that they may be able to strike a balance between the immunogenicity of an attenuated vaccine and the safety of a subunit construct.

## Challenges in developing vector vaccines

Despite the promise of recombinant vector-based HIV vaccines, there are several constraints on the design of these vaccines. Key constraints include the extent to which the additional gene(s) will fit into the vector and how stable the genes will be once inserted. Some vectors will only accommodate short segments of foreign DNA. Additionally, since vectors don't need these foreign genes, they are frequently lost during large-scale production of the modified vector. For example, the envelope gene of HIV has so far proven incompatible with several bacterial vectors.

Another constraint is immunity from prior exposure to the bacteria or virus that is being used as a vector. For example, measles would be a poor vector because almost everyone is already immune to the measles virus, either from getting the disease as a child or being vaccinated as an adult. Thus the body would shut down the infection from the measles vector so effectively that an immune response to the artificially included HIV proteins would not develop. In this respect, a virus like rabies would theoretically be a good vector because most people are not already immune to the rabies virus. In addition, the rabies virus efficiently infects many cell types in humans. But naturally occurring rabies infection is lethal.

So an obvious concern is that the vector itself should not make the immunized person sick. Of course, most viruses or bacteria are isolated and studied precisely because they cause disease. Through genetic engineering, researchers are now working to remove the disease-causing pieces from well-known vectors, while maintaining their ability to infect. However, progress is painstakingly slow.

Another concern unique to HIV vaccines is that they are likely to be used in parts of the world where 10-25% of the population is HIV-infected and serious parasitic and other infections are common. These individuals may be immune-compromised and therefore unable to control the vector infection, even if the vector is perfectly safe in people with normal immune systems. For example, vaccinia, the live poxvirus vaccine, was safe enough to use in hundreds of millions of people as part of the world-wide campaign to eradicate smallpox. However, the use of recombinant vaccinia as a therapeutic HIV vaccine in AIDS patients in France resulted in uncontrolled, disseminated vaccinia infection in at least one patient.

Because of these concerns, the vectors used in HIV vaccines may need to have limited replication capacity. Researchers will need to be sure that immune suppressed HIV-infected recipients will be able to handle exposure to the vector, since it may not be feasible to screen populations in the developing world for HIV infection and exclude them from immunization with an HIV vaccine.

## Immunogenicity of different vectors

A robust infection by the vector in the human host is part of the rationale for exploring live recombinant vector vaccines. Yet remarkably, recent research has shown that even a limited infection cycle can be immunogenic. In a robust infection, the incoming vector invades available cells, completes its life cycle and then begins a second round of infection with progeny produced from the first infected cells. Vectors that do not complete an entire replication cycle but still produce the passenger protein behave like the earliest phase of infection, and some immune responses are induced, even though there is no secondary replication. It is not yet known whether this degree of immunogenicity will be sufficient to provide long-term protection.

Several ways to limit the replicative capability of the vector are currently being explored. One class of viruses, known as avian poxviruses (or avipox) simply do not grow in mammalian cells. Because of this, the avipox viruses (which include canarypox) are being developed as vectors for human vaccines.

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# Vector-Based HIV Vaccines Currently in Development

## *Vaccines in Pre-clinical Research and Development*

| Vector | HIV/SIV content | Developer | Status |
|---|---|---|---|
| Adenovirus | env, gag | Marjorie Robert-Guroff<br>National Cancer Institute, USA<br>Wyeth-Ayerst, USA | chimps/macaques |
| Bacille Calmette-Gurein (BCG) | env-V3 [clades B and E]<br>CTL epitopes | Mitsuo Honda<br>National Institute of Infectious Diseases, Japan | macaques |
| BCG | nef peptides | Bridgette Gicquel<br>Institut Pasteur, France | mice |
| Fowlpox+DNA | env, gag | Stephen Kent<br>Macfarlane Burnet, Australia | macaques |
| Herpes simplex and vaccinia | gp160 | Lynda Morrison<br>Saint Louis University, USA | mice |
| Herpes virus | SIV | David Knipe<br>Harvard/New England Primate Center, USA | macaques |
| Herpes simplex virus | SIV gag | Ann Hill<br>Oregon Health Sciences University, USA | macaques |
| Human rhinovirus | V3 peptides | Gail Ferstandig Arnold<br>Rutgers University, USA | mice |
| Listeria monocytogenes | SIV gag, env | M. Murphy-Corb/Y. Patterson<br>University of Pittsburgh, USA | macaques |
| Modified Vaccinia Ankara (MVA) + gp140 | env, gag-pol | B. Moss, V. Hirsch<br>NIAID, USA | macaques |
| MVA | env, gag, pol, tat, rev, nef | A. Fleuchaus, G. Sutter<br>GSF Institute for Molecular Biology, Germany | macaques |
| MVA | env, gag, pol | Gunnel Biberfield<br>Karolinska Institute, Sweden | macaques |
| MVA+DNA | Multiple genes, CTL epitopes | Andrew McMichael<br>Oxford University, UK | macaques |
| MVA+Fowlpox | env, gag, pol, nef | Therion | macaques |
| MVA+Influenza | core, envelope proteins | Peter Palese<br>Mt. Sinai School of Medicine, USA | macaques |
| Pertussis | gag, nef, V3 peptide | Nicholas Carbonetti<br>University of Maryland, USA<br>Institute of Human Virology, USA | mice, macaques |
| Poliovirus | 220 amino acids of HIV | Raul Andino<br>University of California, San Francisco, USA | macaques |
| Polio replicon | SIV gag, env, nef<br>HIV env (5 clades) | Patricia Fultz<br>University of Alabama, Birmingham, USA | macaques |
| Recombinant polio | peptide fragments | Jeffrey Almond<br>University of Reading, UK | mice |
| Saccharomyces cerevisiae | gp160 | Richard Duke<br>University of Colorado, USA | mice |
| Salmonella (mucosal) | env | Ruth Berggren<br>University of Colorado, USA | mice |

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## Vaccines in Pre-clinical Research and Development *(continued from page 3)*

| Vector | HIV/SIV content | Developer | Status |
|---|---|---|---|
| Shigella | env | David Hone<br>Institute of Human Virology, USA | mice |
| Streptococcus gordonni | gp120 | Simonetta Di Fabio<br>Istituto Superiore di Sanita, Italy | macaques |
| Vaccinia+subunit | gag, pol, env | Shui-Lok Hu<br>University of Washington, USA | macaques |
| Venezuelan equine encephalitis (VEE) replicon | env, gag gene | Robert Johnston<br>University of North Carolina, USA | macaques |

## Vectors In Human Studies

| Vector | HIV content | Developer | Status |
|---|---|---|---|
| Canarypox-ALVAC vCP125 | env | Pasteur-Mérieux-Connaught, France | Phase I |
| Canarypox-ALVAC vCP205 | env; gag-protease | Pasteur-Mérieux-Connaught, France | Phase I, II |
| Canarypox-ALVAC vCP1433 | env; gag-protease; nef/pol | Pasteur-Mérieux-Connaught, France | Phase I |
| Canarypox-ALVAC vCP205 mucosal | env; gag-protease | Pasteur-Mérieux-Connaught, France | Phase I |
| Salmonella typhi (attenuated) | env, gp120 | Institute of Human Virology, USA<br>Johns Hopkins, USA | Phase I |
| Vaccinia | env; gag-pol | Therion, USA | Phase I |
| Vaccinia | 25 different env constructs | St. Jude's Hospital, USA | Phase I |

*Candidate vaccines are made from clade B strains of HIV unless otherwise specified. The information listed above was obtained through a review of scientific articles, abstracts and NIH grants, as well as discussions with a number of researchers. It is by no means a complete list of all vector-based HIV vaccine research. To add information on ongoing research to our database, please e-mail information to: dgold@iavi.org.*

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RECOMBINANT VECTOR VACCINES *continued from page 2*

Another approach is to delete a portion of the genes from the vector. By deleting approximately 10-15% of the genes in the vaccinia virus, researchers have produced an attenuated vaccinia vector. A related approach is to use a vaccinia strain that was "passaged" multiple times in chicken cells so that it barely replicates in mammalian cells. This virus is known as MVA (Modified Vaccinia Virus Ankara).

Still one more approach is to cleverly alter the packaged nucleic acid of a virus so that it can only replicate once in the host. This "replicon" technology is being evaluated in primate experiments for poliovirus and at least two alphaviruses, Semliki forest virus and Venezuelan equine encephalitis virus. Finally, it is possible to bypass the vector completely and just inoculate its DNA. One of the most promising developments has been the surprising immunogenicity of so-called "naked DNA." *[Editor's note: This article does not include DNA vaccines. They will be part of a separate article in an upcoming issue.]*

Although there are many advantages to the naked DNA approach, the biological properties that are unique to the different live vectors could be the key to successful immunization. For example, vaccinia infects a wide range of cell types and generally gets cleared from the body by the immune system, while herpes viruses target the nerves and are able to persist there. Other vectors, such as those that naturally infect the oral/nasal system (adenovirus, influenza, rhinovirus) or the gastrointestinal system (salmonella, polio) mucosa could induce good mucosal immune responses. (Childhood polio vaccines are given orally, and in chimpanzees, an adenovirus-vectored HIV vaccine is being tested through intranasal administration.)

There are still many uncertainties in attempting to design viral and bacterial vectors for use in an HIV vaccine. Researchers still remain fundamentally unsure as to which HIV antigens or specific immune responses are essential for generating protective immunity. Thus, determining the exact HIV genes to incorporate into a vector-based vaccine remains a very open research question. With this in mind, it is clear that the best approach is to encourage the development of a wide variety of vector-based vaccines and move promising approaches into animal studies and well-designed human trials. ◆

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# The Outlook for Leading Vector-Based HIV Vaccines

*by David Gold*

While many recombinant vectors are being examined as potential HIV vaccines, a far smaller number of these vectors have moved into human studies. Listed below is a review of the leading vector approaches that are currently in human studies or could move into human studies in the near future.

**Canarypox:** Canarypox is an avipox virus that has been widely studied as a HIV vaccine vector. Pasteur-Mérieux-Connaught (PMC) has developed a number of different canarypox vaccines (named ALVAC vaccines) that have entered clinical studies in the U.S. and France. The constructs include different combinations of HIV genes. Three ALVAC vaccines have already been in human studies (vCP125, vCP205 and vCP300). Two others (vCP1433 and vCP1452) are about to enter Phase I studies. In addition, a Phase I trial of vCP205 is planned for later this year in Uganda. A Phase II study of the vCP205 construct with a gp120 vaccine began last year in the U.S. Studies administering ALVAC vaccines through mucosal and nasal passages are also planned.

**Outlook**: Support for a Phase III efficacy study of PMC's canarypox vaccine appears to be growing, even among so-called "basic scientists" who might otherwise be expected to oppose the trial. If the Phase II studies of vCP205 and gp120 show some favorable immunogenecity in volunteers, an efficacy study could begin in the U.S. by 1999. Company officials believe that the newer constructs, which include additional HIV genes, will induce broader immune reactions. If this is the case, it will be interesting to see which canarypox vaccines are ultimately proposed for Phase III studies, and whether a more advanced construct can move directly from Phase I to Phase III. The bottom line: key discussions are likely to be about *which* construct to use in an efficacy study and not about *whether* to initiate such a study.

*If the canarypox/gp120 combination shows favorable immunogenicity in Phase II, an efficacy study could begin in the U.S. by 1999.*

**Fowlpox:** Fowlpox is another type of avipox virus that differs only slightly from canarypox. Researchers at the Macfarlane Burnett Centre and the Australian National University are developing a fowlpox HIV vaccine. The vaccine is being used as a boost, in combination with a DNA vaccine. Both the DNA and fowlpox vaccines express the HIV genes *env* and *gag*. Stephen Kent, who heads the effort, reports that, in animal studies, the combination generates better cell-mediated immunity than either vector alone. The DNA/fowlpox combination has also protected macaques from infection with non-pathogenic SHIV. A study using a pathogenic SHIV challenge is now underway. Therion, a Massachusetts-based biotechnology company, is also developing a fowlpox vector vaccine for HIV. The company is planning a combination study using the fowlpox vaccine, with an MVA construct . The fowlpox vaccine includes *gag, pol, nef* and *env* genes, with the *env* coming from primary isolates of HIV.

**Outlook:** Both the Australian and Therion researchers are using fowlpox in combination with a second candidate vaccine. The approach used by the Australian researchers – combining fowlpox with DNA – is unique and bears watching. Therion's strategy of combining fowlpox with MVA is also a creative strategy which may yield interesting results.

**Vaccinia:** Vaccinia-based vaccines use live poxvirus. The poxvirus was safe enough to use in hundreds of millions of people as part of the world-wide campaign to eradicate smallpox thirty years ago. However, an early attempt by French researcher Daniel Zagury to use recombinant vaccinia as a therapeutic HIV vaccine in AIDS patients caused uncontrolled, disseminated vaccinia infection in at least one patient. On the other hand, advocates of the vaccinia approach note that an HIV-infected U.S. Army recruit who mistakenly received the smallpox vaccine developed generalized vaccinia virus but recovered fully without treatment. Therion is developing a genetically attenuated vaccinia product which includes multiple HIV genes. A Phase I study of the vaccinia construct in combinaton with a gp120 vaccine developed by VaxGen, a California-based biotechnology company, is now underway. Another Phase I study of a vaccinia construct recently began at Vanderbilt University and St. Jude's Hospital. This study is evaluating a polyvalient vaccine using vaccinia and 25 different *env* constructs. In addition, Shui-Lok Hu's lab at the University of Washington is studying a variety of vaccinia contructs in combination with subunit boosts in macaques. In the past, Hu's work had been funded by Bristol Myers/Oncogen. It is now being supported by other sources (including a recent U.S. NIH Innovation Grant). Protein Sciences, a Connecticut-based biotechnology company (formerly known as MicroGeneSys), is also reportedly examining development of an HIV vaccine using a vaccinia vector.

**Outlook:** In animal studies, vaccinia vectors have demonstrated impressive immunogencity. When combined with a subunit boost, vaccinia has protected some monkeys against challenge. However, due to the safety concerns, vaccinia's overall prospects as a vector for an HIV vaccine appear to be uncertain. Its primary role may be to demonstrate "proof of concept" protection in animal experiments. On the other hand, two different human studies of vaccinia constructs have recently been launched. If good safety and immunogenicity data emerge from these trials, significantly more resources may be invested in developing vaccinia vectors, at least in industrialized countries.

**MVA:** Modified vaccinia virus Ankara is an attenuated strain of the vaccinia virus that was originally developed by passaging vaccinia in chicken cells. After multiple passaging, researchers found that the virus could no longer infect mamalian cells. MVA vector vaccines for HIV are currently in animal studies in both the U.S. and Europe. Researchers at the U.S. National Institute of Allergy and Infectious Diseases (NIAID), led by Bernard Moss, are planning to evaluate an MVA construct, given alone and

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in combination with an oligomeric gp140 protein, in macaques. The monkeys will be challenged with SHIV 89.6, a pathogenic strain. This MVA construct contains a primary HIV isolate. Researchers at Mt. Sinai School of Medicine in New York are studying an MVA vector used in combination with an influenza vector (expressing core and envelope proteins) in macaques. They believe that the combination will induce strong cytotoxic T-lymphocyte (CTL) responses. Therion is also studying an MVA construct in monkeys and will be challenging them with a pathogenic SHIV strain. The vaccine, which includes *gag, pol, nef* and *env,* will be combined with its fowlpox vaccine (see "fowlpox" above). A research team led by Andrew McMichael of Oxford University is studying an MVA construct in combination with a DNA vaccine. The DNA vaccine is used as a "prime" and the MVA as a "boost." Research teams at the GSF Institute for Molecular Biology in Germany and the Karolinska Institute in Sweden are also studying MVA constructs in macaques.

**Outlook:** While MVA is still in early development and currently has no commercial sponsor, a number of well-respected research teams around the world are developing MVA vaccines. These researchers believe that MVA should have a very favorable safety profile. The NIAID researchers, led by Bernard Moss, appear to be very serious in their efforts. The European groups working on MVA include some of the top researchers in the field. The combination DNA-MVA being studied by the McMichael's team may yield interesting data, particularly in terms of CTL response. Overall, MVA has important advantages as a vector and is being studied in combination with a number of other vaccine constructs. While it has yet to go into human studies as an HIV vaccine, MVA's progress over the next eighteen months could surprise some people.

**Adenovirus:** Adenovirus has been studied by researchers since the 1960s and is currently being evaluated as a vector for both HIV and cancer vaccines. Because it can cause respiratory disease, U.S. military recruits are immunized with a preventive adenovirus vaccine. The vaccine is given in pill form. A well-publicized study, published last year in *Nature Medicine* (3:651-658. June 1997), showed that an intranasal adenovirus vaccine (*env*) given with a gp120 boost provided long-lasting protection against low-dose HIV challenge in chimpanzees. The study was sponsored by the U.S. National Cancer Institute (NCI) and Wyeth Lederle Vaccines & Pediatrics, the Pennsylvania-based vaccine manufacturer. Concerns about using adenovirus as a vector for an HIV vaccine include: Can the vaccine cause adenovirus disease? How extensive is prior exposure to adenovirus and how will that impact the immunogenicity of an adenovirus vaccine? How should an adenovirus vaccine be administered? In chimps, the oral vaccine induced poor immunogenecity while intranasal immunization generated a good immune response. However, intranasal immunization might be capable of causing disease in some instances. One way to address concerns about prior exposure/immunity to adenovirus may be to use two different adenovirus strains in a vector.

**Outlook:** Wyeth appears to be, at best, lukewarm about developing adenovirus HIV vaccines. The company is currently in the process of renegotiating its collaborative effort with the NCI. Wyeth sources suggest that the company's highest priority in the HIV area is DNA vaccines (through its substantial investment in Apollon). NCI officials, for their part, report that while plans for a Phase I study are being discussed, "nothing is imminent."

**BCG:** Bacille Calmette-Gurein (BCG) is a strain of mycobacterium that is used as a tuberculosis vaccine in many parts of the world. Japanese researchers are studying BCG as a vector with just a tiny bit of HIV (tip of V3 using both B and E clades) and CTL epitopes. Mitsuo Honda, who heads the research team developing the vaccine at the Japanese National Institute of Infectious Diseases, told the *IAVI Report* that so far ten macaques have been immunized with the BCG construct. Four of these had "good CTL responses" and three of these were protected against a non-pathogenic SHIV challenge (clade B). According to Honda, human studies of the BCG vaccine could begin within one to two years. The possibility of conducting studies in both Japan and Thailand has been discussed by researchers in both countries.

**Outlook:** Some researchers have high hopes for BCG as a vector. However, others note that with human studies at least one to two years away, it still has a way to go. The work of the Japanese research team is particularly interesting because they are using some non-clade B virus in the vaccine and may initiate trials in both Japan and Thailand.

**Salmonella typhi:** Salmonella typhi (S. typhi) is a bacteria which can cause disease in the gastrointestinal system. What makes it attractive as a vector is its ability to elicit potent mucosal and systemic immune responses in animals. A Phase I study using an attenuated strain of salmonella as a vector in an HIV vaccine recently began at Johns Hopkins University. The attenuated strain was created by deleting certain genes from the salmonella. The current study, a collaborative effort involving researchers at Hopkins, the Institute of Human Virology and NIAID's AIDS Vaccine Evaluation Group, will enroll a total of 44 volunteers. To date, three people have been immunized. As part of the trial, daily blood cultures will be performed on all volunteers.

**Outlook:** While salmonella may induce good immunogenicity, particularly in terms of the mucosal system, safety concerns may make large-scale testing of salmonella vector vaccines difficult. It reportedly took the U.S. Food and Drug Administration three years to approve the current Phase I trial. ◆

AIDS IN AFRICA MEETING *continued from page 1*

conference of leading economic powers in Birmingham, UK in May, 1998.

Also speaking at the conference was the French Minister of State for Health, Bernard Kouchner, who outlined his country's support for HIV vaccine research in general, and IAVI in particular. He also provided further details on President Chirac's proposal for a "solidarity fund" to be established by European and other industrialized countries. Kouchner suggested that a new tax on profits from certain types of capital movements might be used to pay for vaccine research and access to treatment for poor patients in developing countries. He commended IAVI's dual emphasis on scientific research and on establishing mechanisms and incentives to make vaccines available to the developing world.

African researchers also called for a more aggressive and well-funded HIV vaccine development effort. Quarraisha Abdool-Karim, a senior scientist with the Medical Research Council of South Africa and a consultant to IAVI, argued that concrete action must be taken. "We want to see visible and tangible commitments in the area. What has happened since President Clinton's commitment to vaccines and the G-8

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# An Interview with Andrew McMichael

***Andrew McMichael, Ph.D., M.D., heads the molecular immunology group at Oxford University in the U.K. McMichael's research group is focused on the development of HIV vaccines that induce cytotoxic T-lymphocyte (CTL) immune responses. It is also collaborating with a number of researchers in the U.K. and Africa on HIV-related research. McMichael in an internationally -noted immunologist and a member of IAVI's Scientific Advisory Committee.***

**IAVI Report:** Can you tell us about the work your lab is currently doing?
**McMichael:** We have a broad program in basic immunology that underpins our HIV work. And we are particularly interested in the CTL immune response to HIV and whether that response can protect against the virus. We now have several lines of evidence that it can. So we are working on stimulating this response with vaccines.

**IAVI Report:** What type of vaccines are you working on?
**McMichael:** We've been doing experiments in mice to figure out what will best stimulate CTL. We tried peptides, which were not very good. We tried recombinant vaccinia virus, which is quite good in mice and also studied it in macaques. Recently, we've been trying DNA vaccines. In mice, DNA alone stimulates pretty good CTLs. But the combination of "priming" with DNA and "boosting" with modified vaccinia ankara (MVA) is particularly potent at generating CTL response. And Adrian Hill, in this department, is working on trying to get the same kind of immune response with a DNA/MVA vaccine for malaria.

**IAVI Report:** What type of HIV genes have you included in the vaccines?
**McMichael:** We've focused on a string of HIV epitopes. This polyepitope is very good at generating CTL responses. Though we haven't compared it very closely with whole proteins, our impression is that it may be better. In experiments in mice, the polyepitope works brilliantly, every time. The protein construct does not work very well, but there are issues about the expression of the protein that must be addressed before we can say for sure.

**IAVI Report:** What exactly is MVA?
**McMichael:** MVA is vaccinia virus that was grown in chicken cells — over five hundred passages — by Anton Meyer, in Germany, in the 1970s. Out of this multiple passaging came a virus that was highly attenuated. It grows well in chicken cells, but hardly at all in mammalian cells and was used at the end of the smallpox eradication campaign, without any recorded side effects.

What is particularly interesting about MVA is that a number of the deleted genes appear to be immune modulators. For instance, Geoff Smith and Tom Blanchard at Oxford have shown that MVA lacks interferon receptors. In wild type vaccinia these receptors presumably interfere with T-cell response by blocking interferon action, both alpha and gamma. And other cytokine receptors are missing, too. So the absence of these immunomodulating genes may make MVA more immunogenic, despite the fact that it doesn't grow as well. Bernard Moss's group in the U.S. found that MVA was particularly good at stimulating CTL immune responses, which we have confirmed.

*The combination of priming with DNA and boosting with MVA is particularly potent at generating CTL immune response in mice.*

**IAVI Report:** Are all the MVA strains that are being studied the same?
**McMichael:** They're pretty close. They all come from Meyer, although they may have diverged a little since they're being grown in different labs.

**IAVI Report:** If MVA is as immunogenic as vaccinia, why use vaccinia?
**McMichael:** It is not clear to me. Especially because of the obvious dangers in using vaccinia. MVA should not give generalized vaccinia reactions. If you inoculate by scarification (as is done with vaccinia), it doesn't work. MVA has to be administered intramuscularly. There have also been preliminary studies done in immunosuppressed mice without problems. And in terms of immunogenicity, our studies show that MVA works better than vaccinia as a boost.

**IAVI Report:** Where do you think we are in developing DNA vaccines?
**McMichael:** DNA vaccines work very well in mice. But it's not so simple to transfer this into primates or humans. So, we have quite a bit of work to do to optimize the strategy. Initially, our lab had trouble getting reliable and strong CTL responses in mice. By various tricks we were able to sort that out. Now the studies have to be done in primates and humans.

**IAVI Report:** Have you tested the DNA/MVA combination in monkeys yet?
**McMichael:** We've just begun. And we're using both intramuscular and gene gun approaches for the DNA. Our plan is only to challenge the animals that have strong CTL responses. We'll do the immunogenicity tests, priming, boosting and bleeding them, until we get a protocol that gives reliable CTL response. Then we will do challenge studies in macaques.

**IAVI Report:** Do you have a time line for doing the challenge studies?
**McMichael:** It depends on when the immunization studies start working. It could be early spring if the DNA/MVA strategy works the first time. But we may have to go through several cycles, and each cycle takes about four months. So, it could be a couple of years' time.

Our intention is to go to human trials; but not until we have a strategy which we think will work. Setting up Phase I trials is a very complicated procedure, but we're gearing up to do that. And Adrian Hill's team is setting up a Phase I DNA-MVA malaria vaccine trial this year. If that works in humans, we will take the HIV constructs into human studies.

**IAVI Report:** Is it difficult to measure CTL response in macaques?
**McMichael:** It's technically quite hard. The responses are fickle. And at the end of the day, they're sort of semi-quantitative. We're now working with a novel method known as "tetramer binding", which gives a very accurate and simple assay for CTL. This method, developed by Mark Davis and John Altman at Stanford, can quantitate CTL very easily in humans. And we're now doing the same in macaques.

**IAVI Report:** Do you have any doubts that CTL responses are the key to providing protection with a vaccine?
**McMichael:** I'm very optimistic that CTLs will help considerably. But until the right kind of experiments are done, one can't be sure. So far,

these haven't been done because no vaccine strategy induces strong enough CTL responses in animals to do a serious challenge experiment. The few studies where they have been measured suggest quite strongly that animals with high CTLs have lower viral load or may be completely protected.

**IAVI Report:** Are you concerned about designing a strategy that doesn't seek to induce neutralizing antibodies?
**McMichael:** We're focusing on CTLs because that's more than enough for one group. If we come up with a vaccine that gives strong CTL responses in humans we'll go to Phase II and III trials. We would be willing to include a vaccine that reliably neutralizes primary viruses, if there was a good candidate. The ideal experiment would be a Phase III study with all three approaches: inducing CTLs, neutralizing antibodies and both together.

**IAVI Report:** Are there any other recombinant vectors that look interesting?
**McMichael:** There are the pox vectors (canarypox and fowlpox) and some other genetically attenuated vaccinia strains. These are certainly worth looking at and comparing to MVA. There is adenovirus, which I think could be interesting. And many other vectors are starting to be studied. Combining prime -boosts with a third vector could also be interesting.

**IAVI Report:** Some say that animal studies will only tell us certain things and the best way to get answers is by doing a series of human studies. Do you agree?
**McMichael:** I agree with that. But there is a cost part of that equation. In mice, we can do things in large numbers of animals very quickly and rigorously. These protocols can tell us what kind of immune response vaccines make. But there are limitations. And what works brilliantly in mice may not work in primates and/or humans. We know this from a number of examples.

To set up a Phase I study in twenty human volunteers now takes six months to a year. Regulatory approvals are very slow, but obviously necessary. Preparing the vaccine to GMP (good manufacturing practices), recruiting volunteers, setting up facilities, counseling volunteers and testing samples all take time.

In monkeys, you use certain shortcuts. We have quite strict animal testing procedures in the U.K. But, we can test vaccines without GMP requirements, in a range of doses, routes of administration and adjuvants. It's not nearly as expensive as human studies, particularly when testing many different combinations. But yes, we are assuming that what works in monkeys will work in humans and vice-versa, and we don't know that for sure.

**IAVI Report:** Is there an extensive AIDS research effort in the U.K.?
**McMichael:** There is quite an active program. The Medical Research Council (MRC is the national biomedical research agency) had a very broad program, but is now concentrating on a relatively smaller number of groups, of which we are one.

**IAVI Report:** What is the British government's total investment in the area?
**McMichael:** The vaccine program used to get about UK£9 million (US$14 million) per year, about half the MRC's annual investment in AIDS research. And that might be as much as seven percent of the MRC's total budget.

**IAVI Report:** The U.K. has a relatively low case-load of people with HIV. Is there pressure to reduce the government's investment in AIDS research?
**McMichael:** Well, there's certainly no pressure to increase it. The MRC is now focusing on funding work they regard as high quality. If it happens to be in AIDS, that's fine. But if this work didn't really come up to scratch, then it's possible that it would be reduced.

*If CTLs are what is protecting these uninfected sex workers, then the prospects for an effective vaccine are much better.*

**IAVI Report:** Are there other vaccine approaches being studied in the U.K. that you think are significant?
**McMichael:** There is quite a bit going on, although it's much smaller than the U.S. effort. The primate study groups are working with attenuated SIV. They were the first to confirm Ron Desrosiers' findings and are now trying to understand the mechanism of protection. There's a group in Glasgow working on FIV (feline immunodeficiency virus) that is doing a number of interesting vaccine experiments. Frances Gotch, who is now in London, has a vaccine program that is collaborating with a group in Uganda. And SmithKline Beecham is testing a new adjuvant strategy with a gp120 vaccine.

**IAVI Report:** Are you working with any of the vaccine companies?
**McMichael:** We've had discussions with Powderject, which has fused with Geniva (formerly Agracetus). Both companies have gene gun technology and they're now centered in Oxford. The two guns operate rather differently. But it's all under one roof. It's a promising approach for delivery, because one can use much less DNA. In mice, it works really well. As good as, if not better, than intramuscular injection.

**IAVI Report:** Do you think it's feasible to develop an AIDS vaccine?
**McMichael:** I think it's feasible to produce a vaccine that will stimulate strong CTL responses. I'm sure of that. We'll need to move such a vaccine into human studies, even if no clear protection is seen in macaques against intravenous challenge. Remember these challenges use a relatively high dose.

And we need to test a vaccine that really does produce neutralizing antibodies. There's a reasonable chance that either of these approaches, or both together, will prevent infection and reduce virus load in those not completely protected.

**IAVI Report:** Your group is studying "exposed but uninfected" sex workers in Africa.
**McMichael:** Yes. We've done work in Gambia (with Hilton Whittle) and in Kenya (with Frank Plummer). The Kenyan sex workers are more dramatic, because the level of infection is so high, more than ninety percent. Of the ten percent not infected, some will seroconvert, but about five percent are resistant to HIV. And as time goes on, they become less likely to seroconvert, even though every day they are exposed to an average of six partners a day, 20 to 40 percent of whom are HIV-infected. And they have other sexually transmitted diseases which increase the likelihood of transmission.

These individuals are making CTL responses to HIV. But they don't make antibody and they're virus-negative. We, and others, have looked very hard for a protective gene, and we have not found anything like the CCR5/Delta-32 genetic deletion that exists in a small percentage of Caucasians. Yet their cells can be infected with HIV in the lab. So, it looks as if the CTL response is protecting these women. If this is indeed the case, then prospects for a vaccine are good.

**IAVI Report:** Is it more of an acquired protection rather than a natural genetic protection?

*continued on page 12*

# Industry Insider

*by David Gold*

## Apollon Withdraws Public Offering; "Market Conditions" Cited

Apollon, Inc., the Pennsylvania-based biotechnology company, has withdrawn its initial public offering (IPO) to sell stock in the company. Last year, Apollon filed an IPO outlining its intention to sell US$30 million of stock in the company. But on 5 January, 1998, Apollon formally notified investors of its intention to withdraw the stock offering. An official with one of underwriters, the San Francisco-based Genesis Merchant Group, cited "market conditions" as the reason for the withdrawal. The public offering would have set a total value of the company at approximately US$100 million. Apollon is developing DNA vaccines for HIV, herpes hepatitis B and cutaneous T cell lymphoma. Its HIV DNA vaccines include an *env* construct (in Phase I studies), a construct that includes core proteins (in Phase I trial at four U.S. sites) and a combination of the two which will reportedly move into human studies shortly. (See *IAVI Report*, vol.2, no.1, for an interview with Apollon CEO Vince Zurawski.) The company expects to launch Phase II studies of its herpes, hepatitis and HIV vaccines within 18 months. Its HIV vaccine program was developed in collaboration with researchers from the University of Pennsylvania led by David Weiner. Apollon is reportedly also negotiating with the U.S. Department of Defense to jointly sponsor trials of its HIV DNA vaccines in Thailand. In 1995, Wyeth Ayerst Laboratories, a subsidiary of American Home Products, made a substantial investment in Apollon.

## Immuno Drops HIV Vaccine Program

Immuno AG, the Vienna-based pharmaceutical company that was recently purchased by Baxter International, has discontinued its HIV vaccine development program. The company, which operates a substantial blood plasma program, first began its HIV vaccine program in 1986. Led by Martha Eibl, the program focused predominantly on envelope gp160 vaccines. More recently, Immuno had increased its research efforts in the area of whole-killed vaccines HIV vaccines, with plans for animal studies and eventually human trials. The company had been speaking with the U.S. Department of Defense about collaborative efforts in this area. Baxter discontinued the HIV vaccine program in 1997. According to Eibl, the company wanted to focus on "more product-oriented" programs. Baxter's decision is a blow to efforts to increase private sector interest in HIV vaccine development, particularly in the area of whole-killed vaccines, where few companies have expressed any interest. For her part, Eibl will continue most of her research efforts at the University of Vienna, focusing on more basic aspects of anti-viral host defense.

## Vaccines a Good Investment for SmithKline

Vaccine development is a very good business for SmithKline Beecham, according to a recent article in *Forbes* ("SmithKline's Promising Vaccines", 15 December 1997). The magazine reports that vaccines are a "thriving enterprise", generating US$1.2 billion in annual revenues for the world's largest vaccine producer. The U.K. and U.S.-based company expects to increase its vaccine revenues by more than US$1 billion over the next four years. Among its new products are a recombinant (genetically created) vaccine that protects against both hepatitis A and B. SmithKline is also developing vaccines for Lyme disease, herpes, typhoid, respiratory syncytial virus and the bacteria that cause otitis media. In addition, a malaria vaccine developed by the company reportedly looks "very promising". The article makes no mention of any HIV vaccines currently in development. SmithKline's HIV vaccine program is relatively small. However, well-placed sources suggest that the company may be looking to increase its efforts in the area. All told, because of the importance of recombinant genetics, *Forbes* advises investors to "bet on heavily capitalized pharmaceutical companies with deep technology." Such companies include SmithKline, Merck, Pasteur Mérieux and American Home Products, which together account for 85 percent of the world's vaccine business. The high cost of entering the recombinant vaccine market and the ability to patent new technology allows for higher profit margins for new vaccines. In Western countries and Japan, profits on these newer vaccines can total 25 percent of gross sales. But in developing countries, vaccines generally earn little or no profits since companies provide the vaccines at or below cost.

## Leading Companies Meet with NIH About HIV Vaccines

On 23 November 1997, representatives of the four leading vaccine manufacturers met with top NIH officials in Bethesda to discuss the role of the NIH and industry in AIDS vaccine research and development. The meeting was arranged by PhRMA, the influential pharmaceutical trade association. At the meeting, high-level executives from Merck, SmithKline Beecham, Pasteur-Mérieux-Connaught and Wyeth Lederle (American Home Products) met with NIH officials that included Harold Varmus, Anthony Fauci and William Paul. AIDS Vaccine Advisory Committee Chair David Baltimore participated in the meeting by telephone. The industry officials reportedly requested more information on the proposed new NIH vaccine center and its role, particularly in regard to product development. It was agreed that the companies would meet with NIH officials separately to discuss the status of their particular development programs. The first of these meetings is scheduled for January, 1998. According to Gordon Douglas, president of Merck Vaccines (and a member of IAVI's board of directors), the meeting "provided an extremely useful opportunity to exchange information and discuss how we can best complement each other's efforts."

# VACCINE BRIEFS

### Pat Fast Moves to Aviron

Pat Fast, previously the associate director of the Vaccine and Prevention Research Program at NIAID has taken a position with Aviron, a California-based biotechnology company. Fast's new post will be in company's clinical development group. Aviron is developing a number of vaccines, including a live intranasal influenza vaccine which is is now in Phase III studies. The company is also developing vaccines for CMV, and parainfluenza-3. An Epstein-Barr (EBV) vaccine, which is being developed in collaboration with SmithKline Beecham, is now in Phase I studies. The new position enables Fast to return to her native California. During her tenure at NIAID, Fast had a reputation as being extremely knowledgable, hard-working and committed to HIV vaccine development. She built strong relationships with both researchers and members of affected communities. Her full-time presence in the HIV vaccine field will be sorely missed.

### The Important Work of Until There's A Cure Foundation

Until There's A Cure (UTAC) is a U.S.-based foundation that raises funds for AIDS vaccine development, AIDS services and education. The organization, which has distributed grants totaling more than US$2 million, has been an early partner of IAVI, providing important start-up support and funding. UTAC raises funds by selling "The AIDS Bracelet" and has recently expanded its international efforts through partnerships with The Body Shop in Canada, MAX magazine in Germany and others. More than 280,000 people worldwide now wear the AIDS bracelet. UTAC is unique among all AIDS organizations, in that it has strongly supported, from the very beginning, HIV vaccine research and advocacy. If you are interested in purchasing an Until There's A Cure bracelet, call: 1-800-88-UNTIL, fax: 1-650-696-6361, or write: Until There's A Cure Foundation, 520 S. El Camino Real, Suite 718, San Mateo, CA 94402-1726 USA or visit their website: http://www.until.org.

### Vaccine Trial Participants at Higher Risk for Unsafe Sex

Some HIV vaccine trial participants may incorrectly assume they are protected against HIV and engage in unsafe sexual activity, according to a study by researchers at the University of California, San Francisco. The study was published in the *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* (16:266-271. 1997). The researchers, led by Margaret Chesney, followed 48 HIV-negative men and women who participated in Phase I and II placebo-controlled HIV vaccine trials at San Francisco General Hospital a number of years ago. An increase in unprotected anal intercourse from 9 percent at trial entry to 20 percent at the 12-month assessment was observed in trial participants. Researchers also found higher-risk behaviors among younger trial participants, those who had multiple sexual partners and those who indicated that hope of protection from HIV was one of their reasons for joining the trial. Chesney told the *IAVI Report* that she believes trial participants should receive additional counseling before entering the HIV vaccine trials. She also described the counseling efforts in the current Phase II ALVAC205/gp120 study as "excellent and a model for future HIV vaccine trials."

# Help Us Reach More Readers

Dear Reader:

In a very short time the *IAVI Report* has emerged as a vital source of accurate, expert scientific information and news on HIV vaccine research and development.

Published in English and French, and read in nearly 100 countries, the publication is often passed from colleague to colleague and cited in discussions among leading researchers, public health officials, industry scientists, government leaders and members of AIDS-affected communities. Our subscribers include more than 10,000 concerned individuals worldwide who recognize that a safe and effective vaccine represents the greatest hope for a solution to the AIDS pandemic. This is exactly what we had hoped for.

Whether you are involved in research, engaged at the frontlines of public health efforts or working to maintain your health or that of others in the face of HIV-infection, we are glad to have you as a reader.

As always, we welcome your comments – and now, for the first time, we seek your financial help. Please take a moment to help IAVI defray the costs of our publishing efforts. The *IAVI Report* is provided free to all. With your help, we can make it available to additional readers. And if you live in the U.S. your contribution to IAVI, which is a not-for-profit organization, is tax-deductible.

Reaching more readers, especially in developing countries, where over 90 percent of the world's HIV-infected live, is vitally important. Accelerating the global vaccine effort demands a growing number of people who understand the issues and are willing to advocate for the resources that HIV vaccine development requires. This newsletter, and the vital messages it conveys, can help speed progress toward that goal.

Your active readership and support are both crucial to the task at hand: ensuring the development of safe, effective, accessible HIV vaccines for use throughout the world.

Seth Berkley, M.D.
President, International AIDS Vaccine Initiative

# IAVI Announces First Research Awards

The International AIDS Vaccine Initiative announced its first three awards for research projects to accelerate the development of candidate HIV vaccines. IAVI, a global consortium founded in 1996 to ensure development of safe, effective, accessible, preventive HIV vaccines for use throughout the world, awarded funding to the Macfarlane Burnet Centre, the New England Regional Primate Research Center/Harvard Medical School and a collaboration between Boston's Beth Israel Deaconess Medical Center and the Dana Farber Cancer Research Institute.

IAVI is also actively negotiating private sector product development awards with vaccine/biotechnology companies to create public/private collaborations to advance vaccine product development, a critical step in producing HIV vaccines.

According to IAVI Scientific Director Peggy Johnston, "these awards address IAVI's scientific priority: filling critical gaps in HIV vaccine development by supporting promising concepts that have not yet been developed by the private sector." The awards also reflect IAVI's commitment to ensure evaluation of vaccine candidates against the HIV subtypes found in the developing world, where 90 percent of new HIV infections are occurring.

IAVI President Seth Berkley noted that "despite scientific consensus that developing an HIV vaccine is feasible, no candidate has ever been tested for efficacy since the human immunodeficiency virus was identified in 1983. The awards that IAVI makes today will help develop HIV vaccines and address this overwhelming need."

IAVI seeks to accelerate vaccine development by directly funding promising areas of applied research. IAVI also works with governments throughout the world, biotechnology and pharmaceutical companies, public health agencies, non-governmental organizations and others to address the complex political and market issues that have hampered the progress of suitable vaccines, and to educate decision-makers and the public about the need to develop HIV vaccines. IAVI's major funding partners are the U.S.-based Rockefeller, Sloan and Starr Foundations, the Joint United Nations Programme on HIV/AIDS (UNAIDS), Until There's A Cure Foundation and the World Bank. Other IAVI partners include the Mérieux Foundation of France, the National AIDS Trust of the U.K. and the National AIDS Convention of South Africa.

Ronald Desrosiers of the New England Regional Primate Research Center and the Harvard Medical School was awarded US$32,934 over six months to design a large-scale, long-term study of the safety of live-attenuated SIV vaccine in monkeys. (SIV is the simian immunodeficiency virus, which causes an AIDS-like illness in monkeys.) Live-attenuated vaccines, made from a weakened form of living virus, have been effective against many other diseases such as measles and mumps, and have been shown to protect monkeys from SIV infection. Moreover, some humans who became infected with weakened forms of HIV through transfusion have remained healthy with no signs of disease for more than 15 years. Desrosiers' study will seek to provide more extensive data on the safety of this vaccine approach.

John Mills, at the Macfarlane Burnet Centre in Australia, will use IAVI's award (up to US$415,500 over the next two years) to study a DNA-based, live-attenuated vaccine in animal models. This effort will manufacture a weakened SIV DNA that causes infection but not disease, and evaluate its ability to protect monkeys against "wild type" SIV that does cause disease. Vaccines made from "DNA molecular clones" may be better than live-virus vaccines for use in developing countries, since it would likely be less costly to manufacture and transport. An Australian biotechnology company, AMRAD, has been included as a party to this project.

Norman Letvin of Beth Israel Deaconess Medical Center and Joseph Sodroski of the Dana Farber Cancer Research Institute were awarded up to US$494,108 for a two-year joint project to develop hybrid viruses (SIV with an HIV subtypes E and C envelope coating). Such hybrids will be useful in testing whether vaccine candidates might protect against infection by HIV subtypes E and C, which are prevalent in Asia and parts of Africa. Vaccines that elicit broadly protective responses are critically important to developing countries in which multiple subtypes of HIV predominate.

The award winners were recommended by IAVI's Scientific Advisory Committee, which is comprised of twelve distinguished vaccinologists, HIV researchers and other scientists from nine nations. The committee is chaired by Jaap Goudsmit of the University of Amsterdam. ◆

### THE INTERNATIONAL AIDS VACCINE INITIATIVE

The International AIDS Vaccine Initiative (IAVI) is a global initiative founded in 1996 to ensure the development of safe, effective, accessible preventive HIV vaccines for use throughout the world. For further information on IAVI or HIV vaccine development, visit our website at http://www.iavi.org or e-mail us at: info@iavi.org.


## IAVI REPORT

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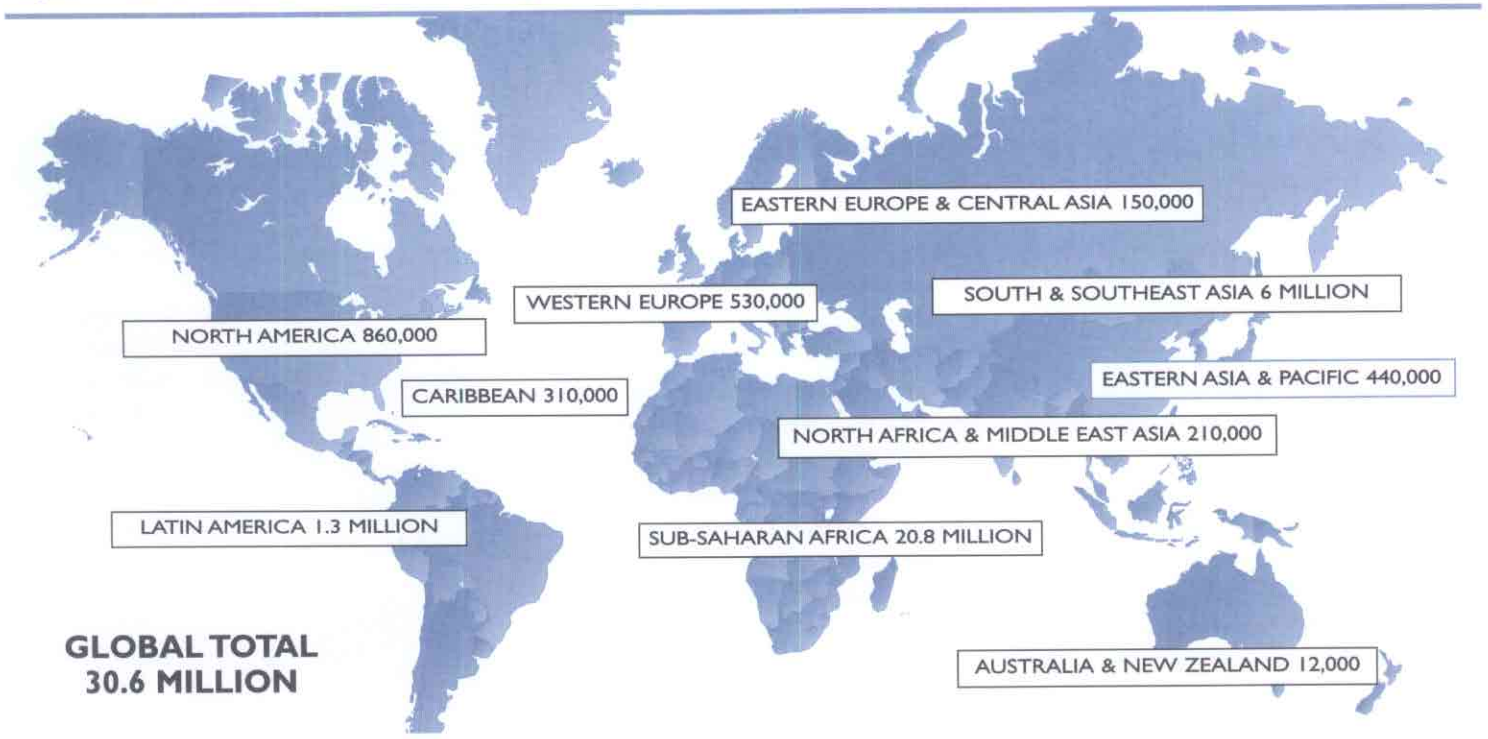
# New Estimates on the Global AIDS Epidemic

**In December 1997, the Joint United Nations Programme on HIV/AIDS (UNAIDS) released a report which contains new and frightening estimates about the global HIV/AIDS epidemic.**




AIDS IN AFRICA MEETING *continued from page 6*

meeting in Denver? Very little. We want something achievable, such as a fund to pay for research and development and to provide incentives to industry."

IAVI officials worked hard to insure that HIV vaccine issues were widely discussed at the meeting. Both Seth Berkley, IAVI's President, and Peggy Johnston, the organization's Scientific Director, addressed the delegates. "We are pleased that, unlike in the past, vaccines are now beginning to be discussed at some of the international meetings," said Berkley. "But we need to take concrete steps to accelerate our vaccine development efforts." Berkley was particularly impressed with the efforts of President Chirac. "In our discussion with the President, we expressed to him our view of how important the efforts of the French government are in the area of HIV vaccine development."

In discussing the state of the research effort, Johnston called for a more concerted effort to move multiple promising candidate vaccines into human trials in both industrialized and developing countries. She said that "there is an urgent need to develop vaccines based on strains found in developing countries and to test them where the need is greatest." No candidate HIV vaccine has yet been tested in Africa.

Berkley noted that "we have no idea what works and until we test HIV vaccine candidates in human subjects, we are unlikely to know. To date", he added, "more than 25 vaccines have been tested for safety in humans and found safe. Yet despite this 17-year history, no HIV vaccine has been entered in an efficacy trial. In my view, that is scandalous."

In addressing the conference, Peter Piot, executive director of UNAIDS, noted that the HIV epidemic now rivals malaria as a killer in the world's poorest continent. "Let me tell you that the epidemic is much worse than we thought," Piot told delegates. "AIDS has already become as big a killer in Africa as malaria. Economic losses due to AIDS may soon outweigh foreign aid in some African countries."

In one of the key scientific presentations at the meeting, Luc Montagnier, the French researcher who co-discovered the virus that causes AIDS, stated that development of an HIV vaccine was possible within a reasonable period of time. According to Montagnier, natural immunity to HIV in a few individuals provides important clues about finding a vaccine against the virus. He suggested that one scientific approach is to test subunit HIV vaccines based on the *nef* gene. If the vaccine can generate an immune reaction to this gene, according to Montagnier, it may be able to protect against HIV. He reported that this strategy has shown promising results in animal studies. ◆

McMICHAEL NTERVIEW *continued from page 8*

**McMichael:** My guess is that there's probably a bit of both. There are probably some favorable genes, but not totally protective. And there is some immune response that seems to protect them.

**IAVI Report:** In terms of the overall HIV vaccine effort, is there anything that you think could be done that is not being done?

**McMichael:** Ultimately, we're going to need to do trials in developing countries, and we'll need groups in these countries that have expertise. So, it very important to establish close scientific collaborations. We're very keen to train Kenyan scientists to work with us, and have already started this process. Building these relationships will be very important. If we fail to do so we will be making a terrible mistake.

Overall, there are many candidate vaccines, but moving them into human studies is a long, slow, expensive process. And you can't try everything. Each lab has to make its choices about what to work with. But the groups doing good research need to be backed. And as we move towards larger human trials it's going to get very expensive. Phase III studies will cost tens of millions of dollars. So, the governments of the wealthier nations must be prepared to provide backing for this effort. ◆