IAVI’s Vaccine Development Partnerships

The cornerstone of IAVI’s scientific program is its Vaccine Development Partnerships (VDPs). Designed to move promising experimental vaccines into clinical trials as rapidly as possible, VDPs link researchers from academia or biotechnology companies with vaccine manufacturers and with clinical researchers in developing countries. In addition to providing funds, IAVI also brings in expertise, as needed, in areas ranging from project management to regulatory affairs and infrastructure for clinical trials.

In choosing which experimental vaccines to move forward, IAVI looks for novel approaches that have shown significant promise in non-human primates and can progress to clinical trials within approximately two years. The candidate vaccine is then tailored to match the predominant HIV strain in the VDP’s developing country (where clinical trials will take place)—a mechanism which ensures that vaccines are developed for the world’s poor nations and not just for the profitable markets in industrialized countries.

IAVI currently has four Vaccine Development Partnerships and is exploring new collaborations linking academic and biotech industry vaccine designers in the U.S. and European Union with clinical researchers in India, China and Africa.

The Oxford/Kenya Partnership: DNA vaccine with MVA Prime Boost

The Oxford/Kenya Partnership is developing a DNA + modified vaccinia Ankara (MVA) candidate HIV A clade vaccine. This effort links the research teams of Professor Andrew McMichael of Oxford University and Dr. J.J. Bwayo of the University of Nairobi in developing two separate vaccine constructs - a DNA vaccine and a modified vaccinia Ankara (MVA) virus vaccine - to be used in combination. Pilot lots of the DNA vaccine are being manufactured in the United Kingdom by Cobra Pharmaceuticals; the MVA vaccine is being manufactured by the German firm IDT.

This project aims to develop a candidate HIV vaccine that can stimulate broad, long-lasting cellular immune responses (cytotoxic T cells, or CTLs) to multiple HIV epitopes from the gag, pol and nef genes. It contains two distinct vaccine components that will be used in a “prime-boost” immunization regimen starting with the HIV-DNA component and followed by a second construct made with a non-pathogenic virus (the modified vaccinia virus, Ankara, or MVA) and the same HIV epitopes. Both components are made from HIV subtype A, the principal subtype circulating in Kenya. Clinical trials will take place first in Oxford, U.K. and then in Nairobi, Kenya, beginning in mid-2000.
The strategy is novel in several ways, first and foremost in targeting the cellular immune response. The rationale for this unusual approach comes from extensive studies of commercial sex workers in Nairobi, where the incidence of HIV infection exceeds 30%. Despite frequent exposure to HIV, a small minority of these women has resisted infection over many years (although a few became infected recently after stopping commercial sex work). By detailed immunological analysis, Dr. Sara Rowland-Jones of Oxford University found that these “resistant” women show significant levels of HIV-specific CTLs circulating in their blood, suggesting that CTLs may play a crucial role in protecting the women against infection. The researchers also found an inverse relationship between levels of CTL and viral load in HIV-infected people, adding support to the idea that CTLs are critical for limiting HIV-mediated disease.

Until recently, it has been difficult to develop experimental vaccines capable of stimulating high levels of HIV-specific CTLs. This partnership is pioneering efforts to demonstrate that a two-step “prime-boost” regimen can overcome this difficulty and generate high levels of virus-specific CTLs.

The AlphaVax/South Africa Partnership: Attenuated VEE Virus Carrying HIV Genetic Material

This partnership is developing a vaccine based on recombinant Venezuelan Equine Encephalitis (VEE) replicon particles (VRP). Inserted into this vector are several genes derived from HIV-1 clade C, the major HIV subtype circulating in South Africa, where clinical trials will be conducted. The partnership links Alphavax, Inc., the North Carolina-based biotechnology firm developing the vaccine, with scientists and clinical investigators from South Africa’s University of Cape Town, National Institute of Virology and Medical Research Council.

Using an attenuated strain of VEE, one third of the VEE genetic material has been removed and replaced with HIV genes. The result of this molecular genetic manipulation is the generation of a self-replicating RNA molecule (called a replicon) that encodes its own enzymes for RNA replication and transcription. The vector is engineered to generate VEE replicon particles (VRP) that are infectious for a single cycle of replication, so that large amounts of HIV proteins are produced but infectious VEE is not (due to the absence of critical VEE structural genes). Most compellingly, preliminary studies with a VEE-based vaccine against SIV (simian immunodeficiency virus) demonstrated significant protection in monkeys against intravenous challenge.

This novel particle vaccine strategy has also been successfully used by Alphavax scientists to produce experimental vaccines against influenza, Lassa fever and Marburg virus.

The Targeted Genetics/Children’s Research Institute Partnership: Single Injection Live Recombinant AAV Vaccine

This partnership is developing a vaccine based on the subtypes of HIV most prevalent in Southern and Eastern Africa, using Targeted Genetics Corporation’s Adeno Associated Viral Vectors (AAV). Their manufacturing process is based on a cell line originally developed by Philip R. Johnson, M.D., Executive Director of the Children’s Research Institute on the campus of Children’s Hospital, Columbus, Ohio.

Dr. Johnson began research on AAV vectors more than seven years ago, with the goal of genetically engineering the vectors to produce specific proteins of medical importance. As a vaccine platform, the idea is to insert key genes from a given pathogen, such as HIV, which in turn should elicit host immune responses similar to those engendered by live attenuated vaccines but without the associated risk of infection with live virus.

Based on preliminary data from non-human primate studies, this approach may provide a long-lived cellular immune response with only a single injection, something which has so far not been achieved with any experimental HIV vaccine. In animal tests of Johnson’s HIV vaccine, the cellular immune response persisted for at least 15 months. These findings provide the basis for moving forward with further pre-clinical development that will support Phase I testing in humans.
This approach is expected to be able to move quickly into human trials because of Targeted Genetics’ previous work on AAV vectors. The company was the first to initiate clinical trials with AAV-based products for use in gene therapy, and so far has treated nearly 60 patients with products based on this technology. Targeted Genetics has successfully dealt with all regulatory issues to date concerning the human testing of AAV-based products and has developed efficient production methods that can be scaled-up to supply large clinical trials and commercial needs in a cost-effective manner.

This experimental vaccine is based on HIV-subtypes A and C, the most prevalent strains in Southern and Eastern Africa and is expected to be field-tested in those regions.

**The Institute for Human Virology/Uganda Partnership: Oral Vaccine Using Salmonella as DNA Vaccine Delivery System**

This project is working to develop a novel type of HIV vaccine that, if successful, will offer significant advantages for use in the developing world. Led by Dr. Robert Gallo at the University of Maryland’s Institute for Human Virology, the vaccine is based on HIV subtype A, which is circulating in many parts of Africa, and will undergo clinical testing in partnership with scientists in Uganda. The vaccine uses a weakened (non-disease causing) strain of Salmonella bacteria as a vector to deliver vaccine DNA into human cells. The cells then translate this DNA into HIV proteins, which in turn stimulate the immune system.

The advantages of this type of vaccine are many. First, it can be produced very inexpensively, and can be given orally -- both key factors for reaching people in developing countries. Furthermore, oral administration is known to induce not only the antibody-producing cells and the cellular immune system, but also the mucosal immune responses that are likely to represent the first line of defense against sexually transmitted HIV. A further advantage of this approach is that bacteria can deliver much larger amounts of vaccine DNA than vaccines based on viral vectors which may enable more HIV genes to be delivered as DNA vaccines by the bacteria. Last but not least, bacteria are highly stable, which should help preserve the quality of the vaccine during shipping and storage around the world.

This approach will incorporate an HIV-DNA vaccine being developed by IAVI’s Oxford/Kenya Vaccine Development Partnership, which is highly effective in stimulating T lymphocyte (cellular) immune responses. Using this already available DNA will enable the Salmonella-based vaccine to enter clinical trials faster and to be compared directly with the Oxford/Kenyan injectable version.