

“Let us not underestimate the resources required to conduct this battle. In this inter-dependent and globalised world, we have indeed again become the keepers of our brother and sister. That cannot be more graphically the case than in the common fight against HIV/AIDS.”

-Nelson Mandela



***Equipment for AIDS Vaccine Trials
Project Budget
&
IAVI's
Mission and Activities***

Budget

Project Title: Initiating an HIV testing and treatment program for sugarcane plantation workers and their families in Uganda

Clinial Equipment Items Needed	Cost (\$US)
1 clinical chemistry automated analyser (includes shipping)	\$43,000
1 hematology - coulter counter (includes shipping)	\$31,000
TOTAL	\$74,000



IAVI MISSION AND ACTIVITIES

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IAVI's MISSION AND ACTIVITIES

As a global organization working to speed the development and distribution of preventive AIDS vaccines, IAVI works in close collaboration with its partners, governments and donors to create a unified voice in support of the aggressive search for a preventive AIDS vaccine and rapid access for all.

AIDS presents an unprecedented challenge. Recent figures released by UNAIDS and the WHO reflect that an estimated 42 million people are currently living with HIV worldwide. AIDS is now the leading cause of death in sub-Saharan Africa, where the disease killed 2.3 million Africans last year alone. In many parts of the developing world, the majority of new infections occur in young adults; young women are especially vulnerable. Roughly one-third of those presently living with HIV/AIDS are aged 15-24 and most of them do not even know they are carrying the virus.

Don't forget Latin America & Caribbean.

In Asia and the Pacific, an estimated 7.1 million people are now living with AIDS. With an estimated 250,000 new infections in 2002, Eastern Europe and Central Asia - especially the Russian Federation - continues to experience the fastest-growing epidemic in the world.

AIDS poses a serious threat to the achievement of all key international development goals, not just those in health. In many countries, it is single-handedly reversing the hard won development gains of the last 50 years.

IAVI believes that a vaccine is the only long-term solution to ending the AIDS epidemic. Our work focuses on four key areas: mobilizing support to accelerate the global vaccine effort through advocacy and education; accelerating scientific progress in applied vaccine product development; creating incentives for industrial participation in AIDS vaccine development; and creating the policies necessary for assuring global access when a vaccine becomes available.

To date, we have invested more than US\$47 million in seven cross-national (multinational?) vaccine development teams, each pioneering one or more promising AIDS vaccine candidates designed specifically for developing countries where the epidemic is most severe.

In the next five to seven years, IAVI will significantly expand its scientific program. We anticipate supporting the development and testing of up to 12 AIDS vaccine approaches - including one or more efficacy trials - by the year 2007. As IAVI's work in developing countries expands, so too does the need for a more comprehensive set of vaccine preparedness activities at the country level directed at engaging and informing government officials, scientists, health professionals, the media, civic and religious groups, and community members. In just the past three years IAVI has:

- Conceived and implemented an innovative public-private AIDS vaccine development model that links scientists in the North with research partners in developing countries;
- Committed vital, multiyear funding for eight promising AIDS vaccine constructs, all based on strains of HIV that are prevalent in developing countries;
- Significantly accelerated the development of two promising AIDS vaccine candidates and launched Phase I trials of these vaccines in the U.K., Kenya, and Uganda;

- Established, equipped and validated a clinical immunology laboratory for the Kenya AIDS Vaccine Initiative (KAVI) team at the University of Nairobi to provide rapid, on-site analysis of blood samples from trial volunteers.
- Built, equipped a state-of-the art Vaccine Trial Unit in Uganda, and recruited and trained local laboratory and clinical staff;
- Begun work to establish additional trial sites in Kenya, Rwanda, and Uganda;
- Signed a Memorandum of Understanding with the Indian Council of Medical Research and the government of India to accelerate development of a vaccine based on the clade C of HIV circulating in India; and
- Signed a Memorandum of Understanding with the Ministry of Health of the People's Republic of China to collaborate in developing one or more AIDS vaccines appropriate for use in China.

AIDS VACCINE RESEARCH AND DEVELOPMENT PROGRAM

IAVI's research and development goal is to ensure that the most promising HIV vaccine candidates are identified, developed, and clinically evaluated for efficacy in the shortest period of time. IAVI's R&D agenda consists of four principal activities:

- Identifying and addressing the primary scientific, development, manufacturing, and clinical trials challenges impeding AIDS vaccine development;
- Increasing the number of AIDS vaccine candidates in clinical trials which are specifically applicable for use in the developing world;
- Accelerating the most promising first-generation (i.e., from among those vaccines currently in clinical trials) vaccines to efficacy trials; and
- Ensuring that second-generation AIDS vaccines (i.e., those currently in development but not yet in clinical trials) provide improvement over first-generation candidates, from the perspectives of safety, efficacy, and applicability for use in the developing world.

To maximize the potential for achieving its mission, IAVI has established Vaccine Development Partnerships and forged a consortium of laboratories focused on designing candidate vaccines that stimulate effective neutralizing antibodies against globally diverse isolates of HIV. IAVI has also established core laboratories and reagent production capabilities to optimize immunologic evaluations of multiple AIDS vaccines from different clinical trials and non-human primate studies.

IAVI's Vaccine Development Partnerships

A vaccine that could stop the HIV virus would yield untold benefit. However, the HIV burden is highly concentrated in developing countries, where annual per capita spending on all health programs typically amounts to \$10 or less. As a result, leading pharmaceutical companies have been significantly deterred from pursuing AIDS vaccines, because a successful vaccine that would be sold primarily to developing countries would not represent a significant business opportunity.

To address this “market failure,” IAVI has developed a unique public-private partnership model. Money donated by foundations and governments worldwide is used to finance and manage research partnerships to develop and test AIDS vaccines, with a focus on those that are specifically designed for use in the developing world. Vaccine Development Partnerships (VDPs) link scientists in industrialized and developing countries with their counterparts in private industry to move promising vaccine candidates from the lab into human trials as quickly as possible. These public-private partnerships represent the heart of IAVI’s scientific program and are part of our global strategic plan to accelerate the search for an AIDS vaccine.

The AIDS vaccine candidates being developed with IAVI’s support are specifically designed for use in developing countries hard hit by AIDS. IAVI-funded vaccines are tailored to match the predominant subtypes of HIV circulating in the developing countries where our clinical trials will take place.¹ And while it should be noted that the significance of viral subtype variability in ultimate vaccine efficacy is as yet unknown (it may be that a single formulation will offer widespread protection against multiple strains), IAVI believes that the answer to this question will only be determined through extensive clinical research. In the interim, we think it only prudent from a scientific standpoint to employ an approach that matches vaccines with circulating HIV strains in order to help ensure that AIDS vaccines are developed for the world’s poor nations and not just for the profitable markets in industrialized countries.

In financing and leading its development teams, IAVI has pioneered a new “social venture capital” model by negotiating groundbreaking intellectual property agreements to help ensure that the fruits of IAVI-sponsored research will be readily available in developing countries at a reasonable price. Starting the R&D process with a guarantee that the eventual vaccines will help the world’s poorest people represents a wholly new approach to vaccine development.

In the past two years, IAVI-funded projects have made tremendous progress in accelerating AIDS vaccine development:

First-Generation Vaccines

➤ Oxford-Kenya VDP: IAVI’s lead vaccine candidate – the DNA+MVA prime-boost AIDS vaccine – has made rapid clinical advances. In a remarkably compressed timeframe, this project has:

- Completed preliminary Phase I AIDS vaccine trials for the DNA and MVA vaccine candidates in both the U.K. and Kenya. Both vaccines demonstrated preliminary safety and immunogenicity.
- Completed a small Phase I trial in Oxford in which the DNA and MVA components were first tested as a prime-boost combination vaccine. This study demonstrated the safety of the MVA in volunteers primed with the DNA component. Data from this trial also confirmed the combination of DNA+MVA to be immunogenic.

¹ HIV is a highly variable virus, with distinct subtypes circulating in different regions of the world: the primary strain in Western Europe and North America is HIV subtype B, with subtype A the most prevalent in east Africa, and subtype C most common in southern Africa and Asia.

- Completed enrolment in a Phase I/II trial in the U.K. in August 2003. This trial is enrolled 119 volunteers at two sites (the Oxford site and at St. Mary's Hospital, Imperial College of Science, Technology, and Medicine in London) to assess the optimal dose of DNA vaccine and interval between the prime and boost inoculations.
- Initiated a trial in the UK and Kenya that aims to determine the best dose and route of injection for the MVA component in individuals who have been primed with DNA. A companion trial, in which the MVA component alone will be tested, has just been approved in South Africa. Additional testing of the DNA and MVA in combination in larger Phase I/II trials is underway in Uganda, and planned for Rwanda.

• IAVI is fast-tracking the DNA+MVA vaccine toward final-stage testing, with the goal of commencing a large-scale efficacy trial in East Africa by 2005, assuming the product meets milestones in intermediate trials over the next two years.

Second-Generation Vaccines

- Targeted Genetics-Children's Research Institute-South Africa VDP: This vaccine is essentially a DNA vaccine in a delivery system based on the capsid of a small, very heat-stable virus called adeno-associated virus (AAV). Preclinical testing has been completed, clinical grade material manufactured, and applications for clinical testing are pending in Germany and Belgium.
- IAVI-Uganda Oral DNA Delivery System VDP: This vaccine is the Oxford-Kenya DNA vaccine packaged in a live attenuated orally delivered bacterial vaccine. Pre-clinical testing of the Salmonella and Shigella vectors is underway. The vaccine is based on the strain of HIV common in East Africa.
- Indian Council of Medical Research-Therion Biologics Corporation VDP: Manufacture of a multigenic MVA vaccine candidate aimed for clinical trials in India is underway, as is preparation of the clinical site in India.
- Aaron Diamond AIDS Research Center-Government of China VDP: Began GMP manufacture of a multigenic DNA vaccine candidate, ADVAX, expressing HIV *env*, *gag*, *pol* and *nef-tat* genes. Phase I clinical trials of this DNA candidate are planned for New York, to begin within the next few months, and subsequently for China.
- Bioption-IAVI VDP: Began vaccine design work on a novel viral vector delivery system termed SFV (Semliki Forest Virus) replicon, an alphavirus vector that has shown promising pre-clinical results. The Bioption project will conduct head-to-head comparisons of two innovative AIDS vaccine concepts based on HIV-1 subtype C to evaluate which combination is most effective. IAVI aims to commence human trials of SFV-based vaccines in 2005 in Asia as well as sub-Saharan Africa.

(See "Attachment A: IAVI's Vaccine Development Partnerships" for more detailed information on each of these VDPs.)

AIDS Vaccine Clinical Trials

Clinical trials are a crucial component of IAVI's vaccine development effort. Because there is no ideal animal model, only the testing of AIDS vaccine candidates in human trials will determine what works – and whether the existing animal models and suspected immune correlates are valid. When testing any candidate AIDS vaccine, IAVI's first priority is to

ensure that the vaccine is safe and will not cause harmful side effects. Moreover, IAVI believes that it is possible to shorten the current time period for vaccine development and clinical trials without sacrificing safety.

At the International AIDS Conference in Durban, South Africa, IAVI released its *Scientific Blueprint 2000: Accelerating Global Efforts in AIDS Vaccine Development*, which outlines a comprehensive global scientific agenda to markedly accelerate the timetable for successful development of safe and effective AIDS vaccines. The *Blueprint* underscores the need to shorten time lines in all facets of the AIDS vaccine development process, but principally in clinical trials design and implementation, vaccine site preparedness and expedited approvals processes. It also highlights the need to conduct multiple clinical trials at the same time and notes that comparative Phase I/II clinical trials of candidate AIDS vaccines offer the best opportunity for rapidly prioritizing vaccines for large-scale efficacy trials.²

To this end, IAVI is working to advance its candidate vaccines into human trials as quickly as possible. To date, IAVI has moved two separate vaccine candidates into Phase I trials in just two years – an unprecedented accomplishment. This is all the more significant when viewed within the context of the many costly and complex development stages required to launch AIDS vaccine trials. These include:

- **Regulatory and Ethical Approvals:** The candidate vaccine and the protocols for the clinical trial must undergo stringent review by national and/or local regulatory authorities and ethical bodies of the countries in which the trials will take place.
- **Strengthening Clinical Infrastructure:** A substantial investment is often required to ensure that an adequate infrastructure exists to conduct clinical trials of candidate HIV vaccines. In preparation for clinical trials in developing countries, it is essential to build a strong laboratory and clinical team, and to strengthen existing laboratory capacity.
- **Building In-Country Laboratory Infrastructure:** While a level of laboratory infrastructure is generally already in place, AIDS vaccine trials typically have additional, critical needs that must be addressed to ensure that all tests are performed in conjunction with accepted standards. This often includes upgrading and improving existing technology and purchasing new lab equipment – such as flow cytometers, centrifuges, plate readers, light microscopes and incubators, which are used to perform a variety of tests to measure immune responses to the vaccine. Clinical chemistry and hematology testing is required for safety assessments. For epidemiological studies and efficacy trials, assays for CD4 counts and HIV-1 virus load must also be established.
- **Site Training:** Good Laboratory Practices (GLPs) and Good Clinical Practices (GCPs) demand adherence to established international standards in areas such as specimen collection, transport, processing, and analysis so that the resultant data will be acceptable for use by licensing agencies. IAVI provides specific training for clinical

² The primary goal of Phase I clinical trials is safety testing, which generally takes 8 to 12 months to complete and involves a small number of healthy, low-risk adult volunteers who receive different doses of the vaccine at different time intervals. After safety has been established, Phase II trials are conducted using more – often hundreds – low- and high-risk volunteers to generate additional safety data and refine dosage levels and administration schedules. Although their chief purpose is to evaluate safety, Phase II trials may also provide preliminary indications of a vaccine's efficacy. With encouraging results, efficacy trials are launched to test the vaccine on many thousands of high-risk individuals to determine its true effectiveness.

investigators in a variety of virology techniques, including standard diagnostic tests, measurement of HIV-1 virus load, and HIV- sub-typing and HLA typing.

- *Community education campaigns* must be conducted in areas where trials will be held to ensure that community members are fully informed about and understand the complexities, aims, implementation and outcomes of the AIDS vaccine trials.

The costs associated with each of the stages outlined above are considerable; the total cost of each Phase I, Phase II or efficacy trial is enormous. For the period FY2003-2008, IAVI has budgeted \$75 million to support Phase I, II and efficacy trials of the AIDS vaccine candidates being developed by our Vaccine Development Partnerships.

Applied Vaccine Research Projects

IAVI is supporting two Applied Vaccine Research Projects aimed at filling critical gaps in scientific knowledge directly related to AIDS vaccine development. These projects will complement our Vaccine Development Partnerships and will be designed to maximize the likelihood of their success. IAVI is initiating these activities through contracts with research laboratories. These projects include:

- **Core Immunology Labs:** IAVI has established two central immunology laboratories to undertake comparisons of different vaccines. One lab is evaluating samples from human vaccine trials and the other is analyzing samples from non-human primate studies. The two labs are using standard reagents and assays that are being validated to industry standards. The human immunology lab is also playing an enormous role in capacity-building, by training developing country researchers from a number of countries.
- **HIV Neutralizing Antibody Consortium:** In collaboration with the National Institutes of Health Vaccine Research Center (VRC), IAVI has formed a consortium of scientists from leading laboratories currently working on neutralizing antibodies. The goal of the consortium is to accelerate the development of candidate vaccines that induce effective neutralizing antibodies against circulating and variable subtypes of HIV.

VACCINE PREPAREDNESS IN DEVELOPING COUNTRIES

Successful and ethical HIV Vaccine trials require the informed and active participation of local communities and broad understanding and support from within the countries in which they take place. IAVI's Vaccine Preparedness (VP) activities extend from preparing for clinical trials to ensuring the eventual uptake of a vaccine.

IAVI is currently working to intensify Vaccine Preparedness efforts in India, Uganda, Kenya, China and South Africa in anticipation of future Phase I, II and efficacy trials.

India: IAVI's Vaccine Preparedness program in India is well underway and includes senior level relationship building, community research and stakeholder education. Recent activities include:

- Engaging the Prime Minister and President in AIDS activities and successfully encouraging them to make AIDS vaccine development a national priority.

- Policymakers from 8 countries attended a Parliamentarians Conference on HIV/AIDS in New Delhi in May 2002. The Indian Prime Minister and other senior politicians inaugurated the event and the “Delhi Declaration,” which calls for resources and commitment to AIDS prevention activities including vaccines, was created and signed.
- The establishment of a senior level advisory board to advise on aspects of vaccine development and access.
- The creation and publication of an IAVI-India newsletter, SANKALP.
- A series of consultations with diverse stakeholders, including: UN Theme Group, civil society, NGOs and others.

Uganda: To support IAVI’s first Phase I/II trial in Uganda (whose protocol was approved in October 2002), efforts have been focused on building relationships and supporting trial recruitment and community education. Key events and ongoing activities include:

- Holding a Parliamentarians meeting on HIV/AIDS in Kampala, Uganda, which spurred the creation of a Permanent Standing Committee on HIV/AIDS;
- Creating and working with a 12-member Community Advisory Board;
- Local media trainings;
- Development of local educational materials;

Kenya: Activities in Kenya are currently focused on preparing feasibility studies and sites selected for clinical trials as well as supporting ongoing Phase I trials. VP continues outreach to various community audiences, including regular briefings with the following:

- Policymakers
- Medical professionals
- Religious leaders
- Journalists and newspaper editors
- NGOs and community organizations
- IAVI is now working to expand its reach in Kenya and build partnerships with a wider variety of organizations and key stakeholders.

China: China’s CDC has expressed interest in AIDS education and communication and other vaccine preparedness activities. IAVI has started the process of developing a work plan which includes sensitizing policymakers, developing community public education activities and materials, and a community level demonstration project.

South Africa: IAVI has developed relationships with key figures within the Government of South Africa and was catalytic in starting the South African AIDS Vaccine Initiative (SAAVI). Additionally, IAVI is working to engage the private sector and has participated in several regional dialogues on ethical issues.

To complement these efforts at the country level, IAVI is also facilitating more effective networking between countries and communities participating in vaccine trials. Lessons learned from these experiences will be disseminated to international policy makers, researchers and NGOs.

ADVOCACY FOR AIDS VACCINE R&D AND GLOBAL ACCESS

Ensuring the development of a preventive AIDS vaccine and global access to it requires more than science alone. It requires global awareness of the need for a vaccine, political will among policy makers and a better understanding of the policies that are necessary at the global, national and local levels to accelerate the search for a vaccine and address key challenges such as financing of research and development, regulatory approvals, manufacturing, purchase, and delivery.

IAVI recognizes the urgent need to increase global political and financial support for AIDS vaccine R&D, and has been working since its inception to ensure that the effort to create an AIDS vaccine gets the requisite resources and attention, without taking away from other critical prevention and treatment needs. Through its advocacy and communications efforts, IAVI is working to ensure that the world invests sufficient funding and political will to develop and test candidate AIDS vaccines as rapidly as possible. One of its key strategies is to explore and promote the creation of mechanisms that will provide financial incentives for industry to play an expanded role in AIDS vaccine development. IAVI also recognizes the importance of establishing and supporting regional and national programs to ensure that developing country voices are a key part of global advocacy efforts.

IAVI's Access Project is working to ensure that once developed, AIDS vaccines will be made available to all who need them without delay. In July 2000 at the 13th International AIDS Conference in Durban, South Africa, IAVI released a blueprint that calls for sweeping changes in the way vaccines are produced, licensed, priced, purchased and distributed. This Blueprint – entitled *AIDS Vaccines for the World: Preparing Now to Assure Access* – represents the first international plan ever to attempt simultaneous introduction of a new vaccine in both developing and industrialized countries.

In the next three years, IAVI will expand advocacy and policy efforts, particularly in the area of policy development and research. The following are major areas of work and key activities planned.

- **Demand Forecasting:** IAVI will launch a well-funded, comprehensive effort to develop reliable data forecasting the potential public health uses and demand for AIDS vaccines. This information is urgently needed to help vaccine developers, health officials and policy-makers understand how vaccines will be used, to ensure that a sufficient supply of vaccines are produced, and to begin planning for financing and delivery.
- **Regulatory Capacity:** IAVI will advocate for – and help develop – policies to insure that developing country regulatory authorities have the capacity to effectively evaluate the safety and efficacy of AIDS vaccines appropriate for their populations. IAVI will collaborate with and support the work of others, such as WHO, that are taking the lead on this effort.
- **Manufacturing Capacity:** IAVI will consult with vaccine developers, manufacturers and public sector donors to identify policy proposals to ensure early and sufficient investment in manufacturing capacity to ensure sufficient global supply of AIDS vaccines as soon as they are available.

To provide guidance in these areas, IAVI has established a Policy Advisory Committee of leading global experts from a range of disciplines and areas of expertise. Members of the Committee will recommend policy actions at the international and national levels to accelerate development of an AIDS vaccine and to ensure swift global access once a vaccine is available.

CONCLUSION

After more than 20 years, we are still plagued by a disease that has overwhelmed global prevention and treatment efforts and is eroding decades of important international development achievements. If we have any hope of stopping the AIDS pandemic, it is in attacking the problem at its root by providing an AIDS vaccine that will protect those most at risk of infection.

In a short time, IAVI has emerged as the leading international organization dedicated to widening the AIDS vaccine development pipeline and reversing the status quo in vaccine distribution. In the past three years alone, IAVI has demonstrated its unique ability to fund, manage and accelerate the development of several promising new AIDS vaccine candidates.

From the beginning, IAVI has worked to build a broad base of support among a range of stakeholders who can join together in helping to overcome the political obstacles to AIDS vaccine development.

IAVI'S VACCINE DEVELOPMENT PARTNERSHIPS (VDPs)

IAVI's Vaccine Development Partnerships continue to make significant progress in achieving key milestones. These projects are summarized briefly below.

Oxford-Kenya

The Oxford-Kenya VDP, launched in late 1998, links vaccine designers in the United Kingdom with Kenyan clinical research scientists for vaccine trials in Oxford and Nairobi. This team, led by Dr. Andrew McMichael of the University of Oxford and Dr. J.J. Bwayo of the University of Nairobi, has developed and is now testing a combination vaccine designed to stimulate strong HIV-specific immune responses. This novel vaccine concept utilizes a "prime+boost" approach combining two vaccine technologies: DNA (to "prime" the immune response) followed by MVA (to "boost" the response). The candidate vaccine is derived from HIV-1 subtype A – the strain of the virus most prevalent in East Africa.

IAVI continues to accelerate this DNA+MVA candidate through human testing in both the U.K. and Kenya. In Oxford, both the DNA and MVA components of the vaccine have been tested separately in Phase I trials. Testing of the DNA and MVA in combination began in October 2001 and represents the first human test ever of a DNA+MVA AIDS vaccine. Phase I trials of the DNA vaccine began in Nairobi in March 2001 and were rapidly fully enrolled. The Kenyan trials are historic in that they represent the first time that human trials are being done *in Africa* using a candidate AIDS vaccine designed for a primary strain of HIV *circulating in Africa*. Approval for the MVA trial was received from the Kenyan government in October 2001 and the trial is currently underway in Nairobi. Phase I/II DNA+MVA trials are underway in Oxford and London. In February 2003, a DNA+MVA Phase I/II trial was initiated at the Uganda Virus Research Institute in Entebbe under the supervision of Dr. Pontiano Kaleebu.

Indications from early trials are that the DNA plus MVA formulations are safe. And preliminary data suggest that the DNA plus MVA stimulates the desired immune response – comparing quite favorably to other candidate AIDS vaccines currently in development. These trials also demonstrate IAVI's unique ability to fast-track the development of promising new AIDS vaccine concepts – moving the vaccine candidate from the lab to the clinic in under two years. If data from the Phase I/II trials are positive, IAVI aims to begin large-scale human testing of this product within three years in Eastern and Southern Africa.

Targeted Genetics-Children's Research Institute-South Africa

Launched in February 2000, this VDP teams researchers from Targeted Genetics Corporation (Seattle, Washington) with scientists at Children's Research Institute (Columbus, Ohio). The genes encoding for the proteins of Adeno-Associated Virus (AAV) are replaced by HIV gene(s) and the recombinant AAV particles are used as a vaccine vector to deliver the HIV gene(s). The project will focus primarily on using HIV *gag* genes from Clade C, the most prevalent HIV strain in Southern Africa, to accelerate entry into clinical testing.

The AAV vector approach has attractive features: natural AAV is not associated with disease in humans, and AAV can persist in human cells and thus a recombinant AAV(HIV) vector could express HIV genes for a relatively long time that would confer long-lasting immunity with a single-dose vaccination. This holds particular promise for use in developing countries. Studies are planned to determine the immunogenicity of a single administration of AAV and to accelerate the development of a prototype recombinant AAV/HIV vaccine for evaluation in Phase I trials. Trials are expected to commence in Q3 of 2003.

IAVI-Uganda Oral DNA Delivery System VDP

The IAVI-Uganda Oral DNA Delivery System VDP, launched in May 2000, is focused on the clinical testing of three promising AIDS vaccine candidates in Uganda. IAVI is collaborating with the Ugandan Virus Research Institute in Entebbe to conduct further tests on the DNA/MVA vaccines that are currently being evaluated in Kenya and the U.K. by IAVI's Oxford-Kenya Vaccine Development Partnership. The Uganda project also includes scientists from the University of Maryland's Institute of Human Virology (Dr. Robert Gallo and Principal Investigator Dr. George Lewis), who will be testing an orally administered vaccine that uses weakened *Salmonella* and/or *Shigella* bacteria as a delivery system. All three vaccines are based on HIV Clade A, the strain predominantly found in Uganda.

This VDP will use a live, attenuated bacterial vector to deliver a DNA vaccine. This bacterial vector delivery system has qualities of particular interest: it can engender potent immune responses, including the potential to generate effective systemic and mucosal immunity, it is administered orally, and it is easily affordable, making it attractive for use in developing countries.

To accelerate the construction of the vaccine and to allow comparisons between different delivery concepts, the bacteria have been engineered to deliver the DNA vaccine developed by IAVI's Oxford-Kenya Partnership. Discussions are underway with manufacturers regarding production of pilot lots of the vaccine for Phase I clinical trials.

A combined Phase I/II dose-ranging and safety trial with *Salmonella*/*Shigella* vectored vaccine will be conducted in the United States at the University of Maryland. The Uganda Virus Research Institute was selected for the Phase I trials in Africa based on its strong commitment to conducting AIDS vaccine trials and the infrastructure previously established through collaborations with the Medical Research Council (MRC) and the Imperial College of Science, Technology and Medicine in the United Kingdom. The plan included building a Phase I clinic with additional laboratory space which is now complete.

Indian Council of Medical Research-Therion Biologics Corporation

In March 2001, IAVI launched its first VDP in India. This VDP is a collaboration between the Indian Council of Medical Research and Therion Biologics Corporation (Cambridge, Massachusetts) to develop a multigenic MVA vaccine based on the Clade C subtype of HIV circulating in India. Designated Indian scientists have visited Therion to participate in the development of the vaccine. This program is unique in that it represents the first time that IAVI will be transferring the technology from an American biotech company to an Indian vaccine manufacturer for production of the vaccine after pilot production has been completed. Pune and Chennai are being considered as potential sites for clinical trials in India and site development activities will be initiated soon.

The clinical trial site for this vaccine is the National AIDS Research Institute in Pune, Maharashtra, headed by Dr. R.S. Paranjape. Manufacturing of this candidate has recently been initiated by Therion, with regulatory submission in India targeted for the 4th Quarter of 2003.

Aaron Diamond AIDS Research Center-Government of China

This project is a partnership between the Aaron Diamond AIDS Research Center (New York, NY), the Chinese Academy of Medical Sciences and IAVI. This VDP is focused on developing a DNA Prime+MVA Boost vaccine strategy (based on HIV subtype C circulating in China), similar to the Oxford-Kenya approach. Phase I clinical trials and comparative non-human primate studies will be used to assess whether this strategy offer advantages over similar approaches.

The first DNA candidate, ADVAX EG-1, expressing HIV *env* and *gag* genes, has been constructed and evaluated in small animals. GMP manufacture of the DNA vaccine will be provided by Vical. A second DNA candidate, consisting of *pol-net-tat* has been constructed and has been shown to be immunogenic in mice.

Phase I clinical trials of the first DNA candidates are expected to begin in the U.S. in 2003. In China, IAVI has held discussions with the Chinese Academy of Medical Science to prepare an immunological testing laboratory and Phase I clinical trial site and with the Chinese Centers for Disease Control to do vaccine preparedness. IAVI has also provided financial support to the State Drug Administration of China to build up their capacity to conduct necessary regulatory work on these new vector candidates.

Biotion-IAVI Vaccine Project

Swedish Biotechnology firm Biotion AB is partnering with IAVI to develop and test a new approach for vaccines that can train the immune system to protect against HIV/AIDS. The vaccines are being built from a proprietary technology, SFV alphavirus replicons, pioneered by scientists at the Karolinska Institute, Sweden's premier biomedical research institution.

The Biotion-IAVI AIDS vaccines will be constructed from Semliki Forest Virus (SFV) replicons. An SFV replicon is a genetically engineered version of the naturally occurring alphavirus SFV, modified so that it does not cause disease, and further modified to include synthetic copies of a subset of HIV's genetic material. The aim is for SFV replicons to deliver HIV genetic material to human cells, in turn stimulating the immune system to

develop defenses against the virus. The vaccines will be constructed to match closely the strain of HIV, subtype C, common in sub-Saharan Africa and parts of Asia. Phase I trials will likely take place in India and potentially other countries in Asia and sub-Saharan Africa.

The Bioption project complements ongoing VDPs and provides a unique opportunity to determine if the SFV technology offers significant advantages over other AIDS vaccine development strategies. It also allows researchers to prioritize this concept compared with other DNA and viral vector strategies currently being developed through other IAVI VDPs.