Report of the Workgroup on Vaccines

Background and Progress Since Coolfont

There currently is no effective vaccine for the prevention of HIV infection. Although considerable progress has been made in overcoming the difficulties associated with preparation, purification, laboratory testing, and formulation of experimental products, formidable problems remain. These include insufficient information about some of the most basic scientific issues:

- virus-host cell interactions;
- mechanisms of immunity to provide protection;
- the extent and consequences of HIV genetic variation;
- the consequence of dormant virus; and,
- an animal model for evaluation of experimental products.

Advances in vaccine development

The PHS supports a multifaceted approach to vaccine development that includes killed and attenuated virus, purified natural or synthetic subunits of the virus, infectious recombinant viruses, and anti-idiotypes. The ideal HIV vaccine is one that would mimic or improve upon immunologic stimuli elicited by natural HIV infection and be fully protective, cause minimal adverse reactions, be highly stable, and be relatively easy to produce and administer.

Although all types of vaccines continue to be evaluated in a series of animal models, the major focus has been on the HIV envelope gene product, gp160, and its cleavage products, gp120 and gp41.

The gp160 molecule contains a number of areas of interest, including the HIV binding site for the CD4 receptor of T lymphocytes. This binding site is thought to be a critical target for the interruption of virus-host cell interaction. Neutralizing antibody binding sites have been mapped to selected regions on gp120. This envelope antigen may be important for induction of protective immunity.

Two experimental AIDS vaccines are being evaluated in FDA approved phase 1 trials in the United States. The first, a product made by MicroGeneSys, Inc., of West Haven, Connecticut, consists of purified HIV envelope protein (gp160) derived from genetic material of HIV using a baculovirus vector. This product is being evaluated at the Clinical Center at the NIH in Bethesda, Maryland, and in the Vaccine Evaluation Units supported by NIH's National Institute of Allergy and Infectious Diseases (NIAID). Early results from these trials suggest some antibody responses to HIV antigen in vaccinated subjects, but the extent and effectiveness of this response remains to be characterized. The second product, developed by Bristol-Myers Company of New York, is a live recombinant vaccinia virus containing the gp160 gene. This product is being evaluated at the University of Washington in Seattle. Results are not yet available.

Progress has been made in several areas of basic science important to vaccine development. Much has been learned about molecular biology and genome organization of HIV. To date, nine genes have been identified. Comparative nucleotide sequence analyses, comparison among different HIV strains, and the identification of conserved and variable regions underscore the importance of experimentally inducing immunity to antigenically distinct strains of virus.

Whether neutralizing antibody, antibody- dependent cell cytotoxicity, cytotoxic T lymphocyte responses, or helper T lymphocyte responses can be effective in preventing HIV infection is still unclear. Scientists agree that an effective AIDS vaccine almost certainly will require the induction of both humoral and cell-mediated immune responses.

Animal models

A major impediment to the development of a safe and effective vaccine against HIV infection is the lack of an animal model. An animal model is essential to achieve a better understanding of the functioning of the immune system in various species that will be used to evaluate candidate vaccines. A greater understanding is required, for example, of cell-mediated immune function in the cat, the ungulate, the lower nonhuman primate, and the chimpanzee.

The chimpanzee has become the animal of choice for challenge experiments, but chimpanzees are not an ideal model for efficacy. Although they can be infected with HIV and generate an immune response, thus far they have failed to develop an AIDS-like disease. Moreover, chimpanzees are a

threatened species and, despite breeding programs supported by the Federal Government, the number of these animals available for AIDS vaccine testing in the United States is extremely limited.

Some chimpanzees inoculated with experimental HIV vaccines have developed either humoral or cell-mediated immune responses, but none of the candidate vaccines have protected chimps from becoming infected when challenged with HIV. In all cases, virus was recovered from circulating peripheral blood cells. The results of these early experiments emphasize the need for standardized reagents, assay systems, and challenge protocols for HIV vaccine studies.

Other animals (cats, cows, rhesus monkeys, etc.) can be infected with other non-HIV lentiviruses, and some will develop symptoms of diseases associated with those viruses. The SIV in rhesus macaques can serve as a strong parallel to HIV for vaccine research. The protein products and organization of the SIV genome are closely analogous to those of HIV. In macaques, SIV infection results in an AIDS-like disease characterized by a wasting syndrome and opportunistic infections. SIV infection is also associated with depletion of the CD4 subset of T lymphocytes, and the immunologic responses of macaques are similar to those induced by HIV in man. This system offers scientists perhaps the best opportunity at present to explore different approaches to the development of vaccines that may be applicable to HIV infection. In a preliminary experiment one of two monkeys immunized with a vaccine made from an inactivated whole SIV virus remained free of infection for 315 days after challenge. Infection of macaques with HIV-2, with production of disease, was reported at the recent IV International Conference on AIDS in Stockholm; these findings need to be confirmed and extended.

Other animal models under investigation include the ungulate lentiviruses and feline retroviruses. These model systems are less like SIV and HIV but can still provide significant virologic, immunologic, safety, and efficacy information that might directly relate to the development of AIDS vaccines.

Clinical trials

Several factors combine to make the clinical testing of AIDS vaccines more complex than any vaccine trials previously undertaken. Early studies indicate that some antibodies may in fact help HIV invade cells of the immune system.

A major concern is the possibility of vaccine-induced immunosuppression. Accordingly, the current phase 1 studies include a very comprehensive immunologic analysis to detect early signs of immune suppression.

A second concern is that persons immunized with candidate HIV vaccines will probably test positive on the ELISA test for antibody. In the current phase 1 studies, volunteers have been issued certificates documenting their participation in a study and affirming that their antibody status is due to vaccination, not HIV infection. Still, they could face difficulties in obtaining insurance, traveling internationally, or entering the military or foreign service. Seroconversion is a major impediment to the recruitment of volunteers for phase 1 and 2 studies.

There is also the problem of very low infection rates. Behavior plays the major role in the spread of HIV, and for ethical reasons, participants in a vaccine trial must be instructed on how to avoid infection. As a result, exposure to HIV may be very low in the study groups.

Amassing a study population for phase 3 efficacy trials of candidate AIDS vaccines presents yet another set of challenges. Phase 3 trials will require the participation of thousands of individuals and may extend over several years. Recruiting sufficient numbers of homosexual men at high risk for infection may no longer be feasible because the incidence of infection in this population has decreased. Although the incidence of HIV infection in intravenous drug abusers continues to rise, this group might not be amenable to long-term followup. The numbers of sexual partners of HIV-infected hemophiliacs are limited. Consideration must, therefore, be given to limiting the number of vaccines chosen for efficacy studies as well as to conducting HIV vaccine trials in a country where the HIV infection rate is higher than in the United States. Variations in HIV strains, as well as sociopolitical considerations, present obstacles. PHS has begun discussions with the World Health Organization (WHO) and other international organizations to plan possible strategies.

Vaccine management initiatives

Four major initiatives have been undertaken in the past 2 years to facilitate the development of a vaccine.

- The NIAID has funded several National Cooperative Vaccine Development Groups. These are

multi-institutional, multidisciplinary consortia designed to unite experienced investigators with a range of skills (virology, molecular biology, structural biology, genetics, and immunology) to explore various experimental approaches. It is hoped that by pooling the expertise of scientists from different disciplines, these groups will be able to generate new strategies for developing vaccines. In addition, a recently constituted component of these groups is the AIDS Cooperative Adjuvant Group--investigators who are addressing the important issue of developing more effective adjuvants to potentiate the immune response to candidate AIDS vaccine immunogens.

- The NIAID Vaccine Evaluation Units, located at six medical research centers nationwide, have been supplemented to prepare for AIDS vaccine testing and will serve as a national resource for the early clinical evaluation of candidate AIDS vaccines (phase 1 and 2 testing). Future plans include further expansion of these units to meet the anticipated needs for AIDS vaccine trials.

- The NIH Reagent Repository serves as a centralized source for key research reagents not otherwise readily available. In the area of vaccine development, these include strains of HIV that can be used to measure group-specific immune responses, a variety of viral gene products such as gp120, and materials for the development of standard challenge assays for animal studies.

- The NIH Plan for AIDS Vaccine Development and Evaluation represents a multidisciplinary framework to facilitate government-industry-academic cooperation in all steps of vaccine development, from basic research to preclinical and clinical development to general availability.

Issues, Goals, and Objectives

Given the projected increases in numbers of HIV infected persons both here and abroad, and the difficulties associated with developing effective drug therapies and effecting behavior change among high-risk populations, the Public Health Service should continue to give high priority to the development of a vaccine for the prevention and control of HIV infection.

Issue: HIV Immunology

The components of the immune system that are necessary to produce an adequate and sustained host response against HIV infection are largely unknown. Additional research in this area is mandatory in order to be able to develop a targeted approach to vaccine development.

Goal: Define the role, in humans, of various immune mechanisms in responding or reacting to HIV infection.

Objectives:

- Expand efforts to delineate the role of all aspects of the immune response (neutralizing antibodies, secretory antibodies, antibody-dependent cell cytotoxicity, cell-mediated immune responses including T-cells and their epitopes, and macrophage function) against and/or in HIV infection.

- Determine the accessibility of HIV and its proteins to the host immune system during natural infection.

- Determine the effect of different routes of infection on the immune response.

Goal: Expand efforts to determine the immunologic consequences of genetic variation for vaccine development.

Objectives:

- Establish a program or programs to determine the extent of genetic variation of HIV proteins and HIV virus strains over time.

- Determine variations in immune responses resulting from genetic variation in HIV proteins and virus strains.

Issue: HIV Structure and Activation

A multifaceted approach to vaccine development is needed. Although early attention has been focused on the gp160 products, other types of candidate vaccines must be explored. In addition, novel approaches to prevent integration of the HIV genome into the DNA of macrophages, T4 lymphocytes, and other cells need to be explored.

Goal: Determine which immunization strategy will provide the most efficient means of inducing protection against HIV infection and disease.

Objectives:

- Enhance efforts to study the mechanisms of HIV activation from the provirus state to active infection.

- Expand efforts to ensure that both laboratory and animal research is exploring all possible vaccine approaches, including active and passive immunization, and including HIV live-recombinant viruses, natural and synthetic subunit viral antigens, and anti-idiotype vaccines.

- Ensure that research is being conducted on adjuvant types and carriers to optimize the immune response.

Issue: Animal Models

A major need of the vaccine development effort is an adequate animal model that can be infected with HIV and develop clinical symptoms of the disease. No such animal model is currently known.

Goal: Expand efforts to develop new animal models for HIV and to extend knowledge about existing animal model systems.

Objectives:

- Explore use of transgenic mice and rabbits as animal models for HIV.

- Expand research efforts on SIV and HIV viruses in rhesus monkeys.

- Expand efforts to develop animal models for other lentiviruses.

- Examine vaccine strategies that have been successful in other lentivirus systems and facilitate the application of this work to the HIV system by maintaining an up-to-date centralized data base for vaccine research.

Goal: Ensure that adequate numbers of nonhuman primates are available for vaccine research.

Objectives:

- Conduct ongoing evaluations to define needs for, and expand where appropriate, breeding programs for nonhuman primates.

- Continue monitoring activities to ensure that chimpanzees and other threatened species are not utilized unnecessarily or for duplicative experiments.

- Ensure that there are programs in place to develop and monitor adequate facilities to house infected and noninfected animals and permit needed studies.

Goal: Further characterize the immune responses in primates and other laboratory animals that might serve as potential models for HIV infection and lentivirus infection.

Objectives:

- Characterize and develop strategies to enhance the immune response in HIV-infected animal models.

- Facilitate development and exchange of reagents for animal model research, with attention to quality control mechanisms.

- Develop a strategy for standardization of virus stocks, reagents, and assay systems used in vaccine research.

Goal: Increase public awareness of the positive benefits of the use of animals in research in making progress against human diseases and of efforts being made to assure that scarce animal resources must be used judiciously and humanely. This is especially critical for HIV vaccine research, for which chimpanzees and rhesus monkeys are so important.

Objectives:

- Conduct a public education and awareness campaign regarding the importance of animal models to AIDS research.

- Participate in Administration and Congressional efforts to define ways to protect the use of animals in research while protecting animals as the subjects of research.

- Continue efforts to ensure the most appropriate acquisition and uses of scarce animal resources and to identify alternative research technologies.

- Continue to enforce the PHS Policy on humane care and use of laboratory animals.

Issue: Preclinical and Clinical Vaccine Development

The most controversial aspect of preclinical evaluation of AIDS vaccines is whether or not it is essential to demonstrate efficacy in an animal model. To date, neither of the two vaccine products in clinical trials has been shown to induce protection against HIV infection in chimpanzees, although immune responses have been noted.

Goal: Enhance efforts to produce an HIV vaccine for human use.

Objectives:

- Establish a vaccine development coordination effort to facilitate information exchange at the PHS level regarding HIV vaccine development.
- Examine existing preclinical requirements and provide appropriate resources for review and evaluation of vaccine candidates.
- Establish collaborations with the private sector for vaccine scale-up and production resources.
- Continue to exercise "fast-track" mechanisms for evaluations of vaccine candidates for human trials.

Goal: Develop criteria for initiation of phase 1 trials and for progression from phase 1 to 2 and 2 to 3, including criteria on the ways animal models should be used in the decision pathway.

Objectives:

- Establish a Vaccine Decision Network Committee, composed of government and non-government scientists to address issues of selecting candidate vaccines for further testing and to establish criteria for the use of limited human resources.
- Continue to develop objective evaluation criteria specific to different types of candidate vaccines.
- Define study designs, implementation capabilities, and information on target populations for vaccine efficacy trials.
- Collaborate with WHO and other appropriate international agencies for the conduct of clinical trials.
- Collaborate with other government agencies, e.g., the Department of Defense, on the conduct of vaccine trials.

Issue: Legal and Ethical Considerations

The development of an effective vaccine against AIDS poses myriad legal and ethical problems. Steps must be taken to ensure the protection of subjects in clinical trials from potential detrimental social effects associated with their participation. Risks and benefits of vaccination must be adequately assessed and communicated to potential subjects, both domestically and internationally.

Although to date manufacturers have been willing to proceed with the development of candidate vaccines, vaccine producers and manufacturers may be reluctant to market an AIDS vaccine in the current climate of strict liability.

Additional legal and ethical issues surround the protection of animals used in vaccine-related research, such as international laws governing the importing of animals and their humane use.

Goal: The processes by which human subjects are protected in vaccine clinical trials, e.g., the informed consent process, need to be reviewed to ensure that issues unique to AIDS vaccines are adequately addressed.

Objectives:

- Assess human subjects review issues identified by vaccine trial centers and institutional review boards (IRBs) in evaluating risks and benefits of the clinical trials.
- Continue to support efforts of vaccine testing centers to minimize risks and provide appropriate protection for human subjects.
- Sponsor/conduct education workshops and other information efforts for researchers, administrators, IRB members, and others concerning protection of human subjects in vaccine trials and related AIDS research.
- Disseminate information to the press, institutions, and IRBs that will assist them in understanding the social risks to trial participants, including the significance of being HIV antibody positive on routine tests as a result of receiving a vaccine candidate, without the individual actually being HIV infected.
- Monitor and support appropriate initiatives that protect confidentiality of research subjects and end possible discrimination against clinical trial participants.

Goal: Collaborate with the appropriate international agencies/organizations to develop mechanisms for the protection of human subjects should efficacy trials be conducted abroad.

Objectives:

- Continue to discuss with other U.S. Government departments and agencies, WHO, and other international organizations the most appropriate manner of cooperation to ensure well-designed clinical trials, in foreign settings, that incorporate internationally recognized principles and processes for the protection of human subjects.

- Assess the infrastructure and resources of foreign governmental and private institutions in preparation for foreign clinical trials in which human subjects can be adequately protected.

- Continue educational efforts that promote understanding of the provisions and applicability of the Department of Health and Human Services' regulations for the protection of human subjects.

Goal: Assess the potential liability problems threatening both clinical trials and eventual marketing of an effective AIDS vaccine, and identify possible solutions.

Objectives:

- Develop an issue paper concerning actual and potential liability problems in clinical trials and in the marketing of AIDS vaccines, and identify possible solutions to problems.

- Continue to monitor efforts of policy-related groups such as the Keystone Vaccine Liability Project, the Institute of Medicine, the Congress, and others with interest in liability problems and remedies.