Chapter 31

NIAID: Programs in HIV Vaccines

According to the latest United Nations estimates, more than 40 million people worldwide are infected with HIV, and the global prevalence of this virus will continue to rise. Historically, vaccines have proved to be the most effective weapon in the fight against infectious diseases, such as smallpox, polio, measles, and yellow fever. Thus, HIV vaccines will provide one of the best hopes to end the HIV pandemic (see also Chapter 32).

To control the alarming spread of HIV, a burning need exists for developing of an effective vaccine that would prevent individuals from becoming infected (http://www3.niaid.nih.gov/research/topics/HIV/vaccines/). Characteristics of a desirable HIV vaccine to control the global spread of AIDS include (i) simple to administer; (ii) inexpensive to produce; (iii) inducing long-lasting immunity; and (iv) effective against all HIV subtypes.

Whereas developing an HIV/AIDS vaccine remains one of NIAID’s highest priorities, it still presents a formidable scientific challenge to researchers. NIAID is supporting HIV vaccine development through fundamental basic research (the discovery phase), preclinical screening and animal model development, product development and manufacturing, and clinical research.

HIV vaccine research has progressed from an early focus on HIV surface antigens, particularly the envelope and the role of neutralizing antibodies, to increased attention to cytotoxic T-lymphocytes (CTLs) in HIV immunity. Many novel approaches to elicit anti-HIV neutralizing antibodies and CTLs are now under investigation (http://www3.niaid.nih.gov/research/topics/HIV/vaccines/research/designs/default.htm).

Major goals of the NIAID-funded HIV vaccine research (http://www3.niaid.nih.gov/research/topics/HIV/vaccines/intro/default.htm#) include:

- **Preclinical Research and Development**
  - Identify and develop promising vaccine candidates in animal models that induce (i) broadly neutralizing antibody; (ii) consistent and high level of cytotoxic T lymphocytes; and (iii) strong mucosal immune responses
  - Evaluate the candidates for immunogenicity, safety, and efficacy in animal models
  - Produce products with the most promise, including those that may not have adequate industry support under good manufacturing conditions, and move these products through the Investigational New Drug (IND) approval process
  - Develop and test new adjuvants and cytokines that will increase the magnitude and duration of the immune response when formulated with or given in conjunction with candidate HIV vaccines

- **Vaccine Clinical Research**
  - Identify a safe and effective HIV vaccine through clinical trials by (i) harmonizing protocols to allow products, dose, and route of administration to be compared; (ii) ensuring safety of volunteers during trials; and (iii) ensuring compliance with the requirements of regulatory agencies
  - Advance knowledge of protective immunity by developing and improving laboratory assays of vaccine-induced human immune responses
  - Collaborate with governmental and nongovernmental agencies that conduct HIV vaccine research to expedite the identification of an effective HIV vaccine

### 31.1 Research Activities

NIAID currently supports preclinical and clinical vaccine research in a variety of areas (http://www3.niaid.nih.gov/research/topics/HIV/vaccines/research/):

- **NIAID Division of Intramural Research Laboratories.** A number of NIAID intramural laboratories conduct basic biomedical research on HIV/AIDS and the immune system.
The Dale and Betty Bumpers Vaccine Research Center (VRC). Laboratories at the VRC that conduct biomedical research to facilitate the development of HIV vaccines.

Vaccine Designs and Concepts. Preclinical and clinical vaccine research is supported in a variety of areas. A list and description of vaccine designs currently being investigated by NIAID-supported researchers can be accessed at http://www3.niaid.nih.gov/research/topics/HIV/vaccines/research/designs/default.htm.

Vaccine Preclinical Toxicology Testing. This program provides information to HIV vaccine researchers on preclinical toxicity testing and preclinical product development to aid in translating research concepts into vaccine candidates suitable for human clinical trial testing (http://www3.niaid.nih.gov/daids/vaccine/Science/VRTT/00_Main.htm).

Animal Models. No ideal animal model exists that can imitate the natural history and pathogenesis of HIV infection and AIDS in the human body because the HIV virus exclusively infects and causes disease in humans. Nonetheless, the data from animal models provide better understanding of the immune responses elicted by investigational vaccines, as well as reassurance of safety, guiding preclinical development and decisions to enter into clinical trials with humans.

Non-human primate studies play a leading role in efforts to develop an HIV vaccine. Scientists are using macaque monkeys infected with simian immunodeficiency virus (SIV), a virus closely related to HIV. This model is useful because SIV in macaques follows, albeit slowly, a similar disease course to HIV, and adequate numbers of animals are available. A potential shortcoming is that SIV and HIV, although similar, are different viruses, so that advances made with SIV need to be verified using HIV. Macaques are being used to evaluate a variety of SIV vaccines of the same types as the HIV vaccines being developed for humans. Because the monkeys can be challenged with SIV after immunization, the vaccines can be evaluated for their ability to protect from virus infection or disease in the monkeys.

A hybrid virus created by replacing the SIV envelope with the HIV envelope but retaining the inner core of SIV virus (called SHIVs) replicates acute HIV infection in macaques and causes rapid disease progression leading to death. Monkeys vaccinated with HIV vaccines are challenged with chimeric SHIV to test the ability of the vaccine to protect from infection with the SHIV viruses.

Scientists are also using a number of different animal models to obtain information that can be applied to HIV. Feline immunodeficiency virus (FIV), transgenic mice that contain part of the HIV genome or coreceptors for viral entry, and severe combined immune deficiency (SCID) mice reconstituted with human immune system cells or tissues are some of the animal models being used to study pathogenesis. Information about different animal models currently used to study HIV/AIDS can be accessed at http://www3.niaid.nih.gov/research/topics/HIV/vaccines/research/animal/default.htm.

Vaccine Assessment. Developing a safe and effective vaccine requires that laboratories analyzing samples from clinical trials follow good clinical laboratory practices (GCLPs). The laboratories use sensitive, accurate, reproducible, and quantitative assays that provide clear measurements of vaccine-induced immune responses to allow data to be compared across multiple sites and the most promising vaccines to be prioritized. To define the correlates of protection, innovative approaches will be required to correlate immune response with vaccine-induced protection.

The central components of vaccine assessment include:

Safety Laboratories. All phases of clinical trials testing and monitoring the safety of a candidate HIV vaccine help to determine how well the volunteers tolerate the vaccine. Routine safety tests include analyses of blood and urine sample that check blood cell counts, hemoglobin levels, kidney and liver functions, as well as screening for infection with syphilis, HIV, and hepatitis B and C viruses. These tests are performed by laboratories that meet Clinical Laboratory Improvements Amendments (CLIA) standards of certification and accreditation by the College of American Pathologists (CAP), standards that are normative for all clinical laboratories in the United States. Similarly, international laboratories performing assays for HIV vaccine trials that meet local accreditation are enrolled in CAP and in external quality assurance programs to ensure performance standards.

PBMC Processing Laboratories. To ensure the highest possible specimen quality among different clinical settings, optimal methods are required to collect, process, ship, and store blood specimens to ensure appropriate recovery, viability, and function of blood cells. Site-associated laboratories separate and cryopreserve serum and peripheral blood mononuclear cells (PBMCs) from blood within 6 to 8 hours after collection by venipuncture. Appropriate sample volumes are optimally handled to perform immunologic evaluations that indicate immune resistance to HIV infection.

End-Point Laboratories. The immunologic objective of HIV vaccines is to elicit effective humoral, cellular, and mucosal immune responses. To assess the effectiveness of the new generation of vaccines, scientists have expended considerable effort into developing and standardizing reliable assays that analyze and quantify...