VACCINE RESEARCH AND DEVELOPMENT

Vaccines are perhaps the most powerful tool available to safeguard public health. Since a vaccine to prevent smallpox was invented in the 18th century, vaccines have been a safe, effective, and efficient means of preventing infectious diseases and have saved countless lives. In recent years, new technologies and new insights into the human immune system have greatly accelerated progress in vaccine research and have created exciting new opportunities to combat a wide spectrum of infectious diseases.

Because the potential to alleviate human suffering by developing new and more potent vaccines is so great, vaccine research is a top priority for Federal biomedical research. Within the Department of Health and Human Services, NIAID has the central role in vaccine research and development. The Institute's broad research programs on all classes of infectious diseases and the organisms that cause them, together with basic research on the immune system, catalyze its comprehensive efforts to create new and more effective vaccines. Many of these vaccine development activities are carried out in collaboration with scientists in government, industry, and at academic institutions. To set priorities for vaccine development, NIAID weighs the severity of a disease and the health benefits a vaccine might generate, and considers the scientific and programmatic opportunities, given the status of scientific knowledge.

The Division of Acquired Immunodeficiency Syndrome (DAIDS) supports the discovery and development of safe and effective vaccines to prevent HIV infection and AIDS worldwide. To reach this goal, DAIDS invests in a comprehensive portfolio of research grants and programs spanning basic vaccine research and preclinical testing of candidate HIV vaccines, through human clinical testing in the United States and internationally.

The Division of Microbiology and Infectious Diseases (DMID) supports a full spectrum of vaccine research to (1) prevent infectious diseases such as tuberculosis (TB), malaria, cytomegalovirus (CMV), group B streptococcus, and chlamydia infection; (2) serve fragile populations such as infants, older people, and immunocompromised people; (3) evaluate novel vaccine approaches such as oral, transcutaneous, and combination vaccines; and (4) improve existing vaccines.

Both DAIDS and DMID support large clinical networks and have vaccine production contracts that provide opportunities to move vaccine concepts into the early stages of clinical evaluation. Infrastructure for regulatory oversight, clinical site monitoring, and data management round out the vaccine development process. In collaboration with the Fogarty International Center, both Divisions support building infrastructure and training for clinical research in the United States and internationally.

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research designed to apply the fundamental principles of immunology to the development of improved vaccines. The Division of Intramural Research (DIR) conducts a wide-ranging vaccine program. Extensive efforts are under way to develop vaccines to prevent diseases with global reach, such as malaria, AIDS, childhood respiratory infections, chlamydia, hepatitis C and E, West Nile, dengue, rabies, and genital herpes. NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC) conducts research that facilitates the development of effective vaccines for human disease, with the primary focus of research being the development of vaccines for AIDS.

Division of Acquired Immunodeficiency Syndrome

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the epidemic, and is one of NIAID's

highest priorities. DAIDS supports exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages through the Innovation Grants Program for AIDS Vaccine Research. Other basic vaccine design and development efforts, including testing in animal models, mechanism-of-action studies, and studies of what human immune responses might correlate with protection against HIV are supported through the HIV Vaccine Research and Design Program. The Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD) is a multi-project program that supports iterative product development and later stage vaccine optimization. Two IPCAVD grantees entered vaccines into human clinical trials in 2004.

To help expedite the development of promising HIV/AIDS vaccines, DAIDS also manages several novel public-private partnerships under a program titled HIV Vaccine Design and Development Teams (HVDDT). These contracts support consortia of scientists from industry and/or academia who have product development experience and who have invented promising vaccine concepts that are ready for accelerated product development. This program uses milestone-driven contracts as a way to encourage more rapid advancement of these vaccine candidates into clinical studies. Nine such contracts have been awarded since 2000. All are moving candidates rapidly through production and preclinical testing. Each of the original four contractors has developed experimental HIV vaccines that have entered human clinical trials. In 2003, three new HVDDT contracts were awarded to Alphavax, Inc., which makes alphavirus replicon-based vaccines; Epimmune, Inc., which makes multi-epitope DNA and modified vaccinia Ankara (MVA)-vectored vaccines; and Progenics Pharmaceuticals, Inc., which makes vaccines based on proteins from the HIV outer envelope.

The majority of NIAID-supported clinical HIV vaccine research is carried out through the HIV Vaccine Trials Network (HVTN). Now in its fifth year, HVTN is a global network of clinical sites designed to address the scientific and public health needs of HIV vaccine and clinical research. HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. The network's global capacity allows for rapid expansion as vaccine candidates enter the pipeline for testing and development, and for carrying out large-scale studies of the most promising preparations. The participation of international sites and the involvement of diverse populations through partnership with host country researchers, governments, and communities are critical components of NIAID's HIV vaccine effort. They allow for studies that examine differences resulting from HIV diversity, human genetic variations, nutritional status, the effects of other infections, and differences in access to healthcare—all of which may prove crucial to developing an effective vaccine that can be used around the world. In particular, the international capacity of the network facilitates studies of various HIV subtypes that may affect only a minority of the population, but may be important to the development of a vaccine that will protect people from different circulating strains of the virus.

During the past year, HVTN has initiated or continued several HIV vaccine studies. One candidate under investigation, in trial HVTN 040, is a novel noninfectious Alphavirus replicon HIV-1 subtype C vaccine designated AVX101 and made by Alphavax, Inc. The trial, which is being conducted at sites in the United States and South Africa, is the only one of its kind currently testing this kind of vaccine, which is based on a weakened Venezuelan equine encephalitis virus engineered to contain the HIV *gag* gene.

The first preventive HIV vaccine trial conducted at multiple international sites, HIVNET 026, has been successfully completed. This study evaluated the immunogenicity and safety of a canarypox virus engineered to express HIV proteins (ALVAC-HIV vCP1452) alone and

in combination with a recombinant form of the HIV coat protein (MN RGP120). It enrolled 160 participants; 40 each from Haiti, Trinidad, Brazil, and Peru. Preliminary data from the study confirmed the safety of the approach and provided additional information on the immunogenicity of this vaccine combination.

Collaboration and Partnerships

The AIDS Vaccine Research Working Group (AVRWG) assists NIH in developing a comprehensive research program to expedite the discovery and development of an HIV/AIDS vaccine. The members of the group provide technical assistance to NIH to help assess scientific opportunities, gaps in knowledge, and future directions of HIV vaccine research. As a working group of the NIAID AIDS Research Advisory Committee, the AVRWG makes recommendations to the Directors of NIAID and DAIDS concerning key scientific questions in vaccine development, including new vaccine designs, the mechanisms of protection in animal models, and potential new targets for vaccines.

A formal collaboration for HIV vaccine research, development, and testing between NIAID and the U.S. Army Medical Research and Materiel Command (USAMRMC) was established in 2003 through an interagency agreement with the Department of Defense (DoD). This collaboration helps to ensure that U.S. Government HIV vaccine research is well coordinated, efficient, and comprehensive. The collaboration gives NIAID greater access to the USAMRMC HIV/AIDS research program focused on vaccine product development and to DoD's extraordinary medical infrastructure, as well as to its extensive experience in establishing and supporting operations in underdeveloped regions.

Two vaccine trials have been initiated as part of this collaboration. The first is a phase III study, RV144, which began in Thailand in September 2003. This trial will evaluate an HIV vaccine strategy known as "prime-boost," a combination of two different vaccines. One component is an engineered virus, ALVAC-HIV, while the other, AIDSVAX B/E, is based on purified HIV coat protein. These vaccines are designed to work together to activate both the cellular and antibody-producing arms of the immune system. The second study, RV151 is a placebo-controlled trial to evaluate three escalating doses of a novel candidate vaccine (LFn-p24), designed to induce strong and persistent cellular immune responses to HIV.

NIAID has led the development of the Partners in AIDS Vaccine Evaluation (PAVE) program, which plans and harmonizes clinical trials conducted by the Federal Government. Members include DAIDS, VRC, HVTN, the Centers for Disease Control and Prevention, and the U.S. Military HIV Research Program of the Department of Defense. PAVE is part of a global effort to share information and to increase operational efficiencies in HIV vaccine research and development. PAVE members also expect that working collaboratively to evaluate HIV/AIDS vaccines will foster scientific achievements that a single organization or institution would not be likely to accomplish on its own.

In the past year, the Gates Foundation and NIAID have sponsored a series of meetings to develop a strategic plan for the Global HIV Vaccine Enterprise. The Enterprise is a voluntary consortium of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS. At a recent meeting of G-8 leaders, President Bush announced that the U.S. Government would support the areas of research identified in the Enterprise strategic plan. NIAID has solicited applications for the creation of a Center for HIV/AIDS Vaccine Immunology (CHAVI) to be funded in FY 2005. CHAVI will support an intensive, multi-resourced, coordinated, consortium approach to address key scientific roadblocks in the creation of a safe and effective HIV vaccine for worldwide use. The goal is to

establish a highly collaborative, cooperative and interactive team of leading researchers who will devote the majority of their time to the application of state-of-the-art immunological tools toward this end.

Future Plans

DAIDS is moving to restructure its clinical research program by re-competing all of the current research networks, including HVTN, in 2006. The reorganization process is designed to develop a more efficient and highly collaborative clinical trials network that will enable DAIDS and its partners to meet future research challenges. DAIDS staff will continue to work with HVTN to expand the capabilities and capacity of existing international sites and to develop new sites. Extensive plans are underway to conduct multiple phase II trials of vaccine candidates in multisite studies that include both U.S. and international units; the preparations will focus on infrastructure development, technology transfer, and training.

In collaboration with Merck, Inc., the HVTN is currently conducting a "proof of concept" phase IIb HIV vaccine trial to evaluate the efficacy of a candidate called MRKAd5 HIV-1 gag/pol/nef, an adenovirus-based vaccine designed to prevent infection or delay HIV disease in 1,500 high-risk volunteers. The study will be conducted in the United States, the Caribbean, and South America.

A new Vaccine Developmental Resources Group (VDRG), consisting of internal NIAID staff and external scientists, will be established in 2005. This group will assist DAIDS staff in designing and reviewing protocols for the Simian Vaccine Evaluation Units, which carry out preclinical evaluation of vaccine candidates in nonhuman primates. VDRG will also assist NIAID in assessing the need for government support to advance promising candidate vaccines into and through clinical testing. NIAID will also continue to work within the Global HIV Vaccine Enterprise to help ensure that the Enterprise scientific plan is implemented and will help to update the plan as needed.

Division of Microbiology and Infectious Diseases

Research leading to new and improved vaccines has long been a high priority for DMID. The goal of the DMID Program for the Accelerated Development of Vaccines, established in 1981, is to support research leading to vaccines that will improve health. DMID sets its priorities for vaccine research on the basis of the morbidity and mortality associated with each infectious disease, critical evaluation by the Institute of Medicine (IOM) of the National Academy of Sciences, assessment of research gaps and opportunities, and recommendations made by the National Vaccine Advisory Committee and other advisory groups.

DMID designs and implements a comprehensive research program to develop new or improved vaccines. Advances in microbiology, immunology, biotechnology, and other fields are applied to the development of new vaccines and to the improvement of existing vaccines, including:

- New vaccines against major diseases caused by respiratory syncytial virus (RSV); malaria; group A and group B streptococci; and other bacterial, parasitic, and fungal infections of both children and adults;
- Improved vaccines against diseases such as influenza virus, viral hepatitis, and TB;
- Vaccines to prevent neonatal infections such as group B streptococcus, and congenital diseases caused by CMV infection, toxoplasmosis, syphilis, gonorrhea, and chlamydia infections;
- New vaccines to prevent and control emerging diseases, including *Helicobacter pylori*, West Nile virus, severe acute

respiratory syndrome (SARS), and drug-resistant bacteria such as pneumococcus; and

- Novel technologies that enhance vaccine effectiveness, such as adjuvants, proteosomes, and plasmid DNA approaches.

Vaccine development is a long process, and is often done in collaboration with researchers in the pharmaceutical industry and academic laboratories. Vaccines are first screened for potential safety and efficacy in preclinical studies, including experiments using cell cultures and animal models. If the candidate vaccine looks promising, it may be evaluated in human clinical studies through the DMID Vaccine Evaluation Network, which includes the Vaccine and Treatment Evaluation Units and other units at universities across the United States. An integral part of NIAID vaccine research efforts, these vaccine units support carefully planned human clinical trials of novel bacterial, parasitic, and viral vaccines and other biologics in people of all ages and risk categories. DMID also supports research to develop new vaccine approaches that:

- Generate long-lasting protective immunity to various infectious agents;
- Favor the development of mucosal immunity or the production of a specific antibody;
- Increase the immunogenicity of candidate vaccines or favor the expression of a cell-mediated cytotoxic immune response; and
- Simplify immunization regimens to reduce the number of immunizations required for protection.

In addition, DMID supports vaccine research for emerging infectious diseases, including avian influenza and SARS.

DMID is internationally recognized as an effective participant in vaccine research and development issues with both U.S. and global impact. In the United States, DMID collaborates with other federal agencies, including CDC and the Food and Drug Administration, on issues of vaccine research, vaccine safety, and national immunization strategies; this collaboration is coordinated through the National Vaccine Program Office (NVPO). Internationally, DMID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization and the Multilateral Initiative on Malaria. DMID, together with the World Health Organization (WHO), U.S. Agency for International Development (USAID), Children's Vaccine Program at the Program for Appropriate Technology in Health, Wyeth Vaccines, and the London-based Medical Research Council, currently supports a randomized, controlled phase III efficacy trial in The Gambia, West Africa, to evaluate a pneumococcal conjugate vaccine manufactured by Wyeth containing nine separate antigens; the trial is designed to determine the impact of the vaccine on childhood pneumonia, which is a major cause of mortality in children under 5 years of age in this region.

The evaluation of vaccine safety is an integral component of the DMID vaccine research program. Safety is evaluated in every vaccine clinical trial sponsored by DMID; all participants are monitored closely for any adverse effects of the vaccinations they receive. Specific safety issues such as the use of novel cell substrates for vaccine manufacture and the evaluation of combination vaccines are explored through scientific consultation with other Federal agencies and in coordination with NVPO.

DMID also funds research to better understand safety of the vaccine preservative thimerosal. Since the 1930s, thimerosal has been added to some vaccines and other products because it kills bacteria and prevents bacterial contamination, particularly in multidose containers. When thimerosal is degraded or metabolized, one product is ethyl mercury, an organic derivative of mercury. Little is known about the effects of thimerosal exposure on humans and how it

compares to methyl mercury exposure, another organic mercury derivative. To learn more, DMID has initiated several research activities aimed at better understanding what happens to thimerosal once it is introduced into the body and how this compares to current knowledge of the pathway that metabolizes methyl mercury. DMID supported initial studies at the University of Rochester and continues follow-up studies in Argentina to measure mercury in blood and other samples from infants who received routine immunizations with thimerosal-containing vaccines. In addition, DMID and the National Institute of Environmental Health Sciences are cosponsoring a study in infant macaques to examine the pharmacokinetics and tissue distribution of thimerosal (given by injection) or methyl mercury (given orally). This study will address whether the exposure levels established as safe for methyl mercury are also appropriate for exposure limits on ethyl mercury.

In order to address concerns regarding specific vaccine safety issues, NIAID and CDC requested that the IOM establish an independent expert committee to review hypotheses regarding possible relationships between specific vaccines and adverse events. In response, IOM created the Immunization Safety Review Committee in September 2000. This committee reviews the state of knowledge about various specific immunization safety concerns and communicates its findings to healthcare providers and the public. In the past 3 years, the committee has met to review several important vaccine safety issues, including measles-mumps-rubella vaccine and autism, thimerosal-containing vaccines and neurodevelopmental disorders, multiple immunizations and immune dysfunction, hepatitis vaccine and neurological disorders, SV40 contamination of polio vaccine and cancer, the potential role of vaccinations in sudden unexpected death in infancy, and influenza vaccine and possible neurologic complications. Within several months of each meeting, the committee publishes reports of its findings and makes recommendations about any additional actions that might be indicated.

DMID will continue to apply the latest advances in the fields of immunology, microbiology, and biotechnology to the development of new or improved vaccines against infectious diseases. Some recent applications of new technologies to vaccines include:

- Use of recombinant DNA technology for the production of defined immunogens as well as the preparation of plasmid DNA vaccines;
- Development and use of various immunomodulators to augment the immune response to poorly immunogenic candidate vaccines;
- Development of novel vaccine delivery systems to promote long-lasting immunity or to generate an immune response in a specific host tissues; and
- Research on novel approaches to the development of multicomponent vaccines and simpler vaccination regimens to reduce healthcare costs and the number of visits to healthcare facilities.

Division of Allergy, Immunology, and Transplantation

DAIT supports research on immunologic mechanisms and novel technologies applicable to vaccine design and development. The Division funds vaccine-related research projects on innate and adaptive immunity that aim to increase our ability to manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity. Basic research topics that sustain vaccine development include innate immune receptors for pathogen molecules, antigen processing and presentation, the development of antibody and cellular immune responses, and the elaboration of immunologic memory. Topics more immediate to vaccine

applications include the development of new adjuvants to enhance immunity, the design of approaches that can induce protection in mucosal tissues, and the discovery of new ways to more effectively deliver immunizing agents. Other research that lays the groundwork for improved vaccines includes discovery of new pathogen epitopes—molecular structures of bacteria and viruses that stimulate immunity—and analyses of how variability in the human genome affects immune responses.

DAIT continues to fund four Vaccine Immunology Basic Research Centers that focus on the fundamental aspects of human protective immune mechanisms in infectious diseases. In addition, DAIT's Human Immunology Centers of Excellence Program supports many mechanistic studies that will contribute to our basic understanding of human immunity and vaccine responses.

In FY 2002, the Hyperaccelerated Award/ Mechanisms in Immunomodulation Trials research program was expanded to support in-depth study of immunologic mechanisms during clinical trials of vaccines, including analyses of the underlying mechanisms of protective immunity, specificity and kinetics of immune responses, and immunologic memory. Studies proposed under this program must make use of clinical samples from a clinical trial supported by other funding. For example, NIAID recently funded research to analyze the cell-mediated immune responses of participants in a smallpox vaccine clinical trial.

DAIT has established a program called Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines, which supports several research projects on hepatitis C, tuberculosis, malaria, and HIV. For example, investigators funded through this program recently made a large step toward an effective malaria vaccine when they managed to predict which fragments of various malaria parasite proteins would bind to most members of a class of immune system receptor molecules called the major histocompatibility complex (MHC); only these malaria protein fragments, called supertype antigenic epitopes, can activate the immune system to fight the parasite. The investigators also used proteomic and genomic techniques to select 27 genes expressed in different life stages of the malaria parasite candidates upon which to base a new malaria vaccine. They found that 16 of these 27 candidate genes contained supertype epitopes that were recognized by T cells from individuals vaccinated against malaria, but not by T cells from control individuals. Furthermore, some of these novel antigens stimulated the immune system more vigorously than any of the antigens that are the basis of experimental vaccines previously in clinical trials.[67] This approach will be invaluable in the discovery of vaccine candidates for other diseases as well.

Also under this program, DAIT supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human MHC molecules and the protein fragments that bind them. The database specifies the amino acid sequences of peptides derived from viral, bacterial, parasite, and human proteins in association with human MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to identify specific amino acid sequences that bind MHC molecules. The database is funded through a contract with the University of Oklahoma; further information is available at *hlaligand.ouhsc.edu*.

Grants funded under the Cooperative Centers for Translational Research on Human Immunology and Biodefense Program will facilitate the translation of research results from animal models such as the mouse into studies in humans. This program will develop new technologies to study human immune responses and regulation, and will fund research on human immune responses to NIAID Biodefense Category A, B, and C priority pathogens.

Contracts awarded under the Innate Immune Receptors and Adjuvant Discovery Program will support research on new adjuvants—additives that help stimulate human innate immune responses—from initial evaluation through preclinical testing. The adjuvant products developed under this program might be used both as vaccine adjuvants—to elicit T and B cell responses when co-administered with an immunogen—and as stand-alone immunomodulators—to stimulate short-term protective responses against many different infectious agents.

The Large-Scale Antibody and T Cell Epitope Discovery Program supports the rapid identification and verification of the specific molecular structures on pathogens, called epitopes, that antibodies or T cells recognize during the immune response. A related effort will establish a comprehensive centralized database to provide a Web-based, searchable source of information on pathogen epitopes for researchers. Included in the database is an analysis resource to facilitate data analysis and prediction of novel pathogen epitopes.

The NIAID Tetramer Facility produces MHC/peptide reagents that help detect T cells with different response characteristics; this program, which is also funded in part by the National Cancer Institute, has so far provided more than 1,900 tetramers to investigators worldwide. Reagents are provided for the study of T cell responses relevant to vaccine research and development for many diseases including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at *www.niaid.nih.gov/reposit/tetramer/index.html*.

Division of Intramural Research

DIR is working to develop vaccines against many infectious agents. This work often involves collaborative research and development efforts that span years—or decades—before coming to fruition. For example, FluMist, the intranasal influenza vaccine, is the result of more than 20 years of collaborative research involving Dr. John Maassab of the University of Michigan School of Public Health and DIR scientists, with support from DMID. In addition, DIR has a long-term collaboration with scientists at the Johns Hopkins University to develop and test experimental vaccines against pandemic influenza, parainfluenza, respiratory syncitial virus (RSV), and the RSV-like human metapneumoviruses. DIR scientists also are working collaboratively to develop vaccines against SARS, multiple hepatitis viruses, rotavirus, and several members of the flavivirus family, including West Nile virus, St. Louis encephalitis, and dengue.

Dengue, for example, is a mosquito-borne virus that causes an estimated 50 to 100 million cases of dengue fever and several hundred thousand cases of potentially fatal dengue hemorrhagic fever each year. Four subtypes of dengue virus exist; infection with one subtype does not provide immunity to the others, so persons living in dengue-endemic areas can be infected by each subtype during their lifetimes. DIR scientists are developing a recombinant live-attenuated dengue virus vaccine that would provide protection against all four dengue subtypes. Components of this vaccine are currently undergoing phase I and II clinical testing.

DIR scientists are also working on a several other vaccines. The West Nile virus vaccine developed by DIR scientists will begin phase I clinical testing in 2005. In a collaborative effort with scientists from the military and industry, a hepatitis E vaccine developed by DIR researchers is undergoing clinical trial in an area where the disease is endemic. This work has recently been enhanced by the development of an ELISA test that measures neutralizing antibodies to hepatitis E virus, which will allow faster evaluation of the results of vaccine trials.

The Malaria Vaccine Development Branch (MVDB) is a large DIR program that maintains

collaborations with researchers in the United States and throughout the world; it also works closely with a variety of funding agencies, including the USAID and the Malaria Vaccine Initiative sponsored by the Bill and Melinda Gates Foundation. The MVBD is now preparing several malaria vaccine candidates for clinical testing. One of these is based on the *Plasmodium falciparum* antigen AMA1; see the malaria section on page 100 for more information.

Traditionally, identification of potential new vaccine candidates has been a slow and laborious process, with testing carried out one gene or protein at a time. Now, however, genome sequencing and other high-throughput analytic techniques provide far more rapid methods to identify the parts of an infectious agent that might form the basis of human vaccines. DIR scientists are using these modern tools to identify potential vaccine components for group A streptococcus, *Mycobacterium tuberculosis*, and other agents that cause significant morbidity and mortality worldwide.

Vaccine Research Center

The role of VRC is to stimulate multidisciplinary vaccine research and to translate basic research into candidate vaccines ready for clinical trials. After September 11, 2001, the biodefense role of VRC expanded to include development of preventive and therapeutic vaccines for potential agents of bioterrorism.

The VRC is very involved in the search for an HIV vaccine. In November 2002, the VRC launched a phase I clinical study of a novel DNA vaccine directed at the three most globally important HIV subtypes, or clades. The vaccine, developed by the VRC, incorporates HIV genetic material from clades A, B, and C, which together cause about 90 percent of all HIV infections around the world. This is the first multigene, multiclade HIV vaccine to enter human trials and marks an important milestone in the search for a single vaccine that targets U.S. subtypes of HIV as well as clades causing the global epidemic. The first phase of the trial is being conducted by the VRC on the NIH campus and is designed to determine the vaccine's safety at three dose levels, and to evaluate how well the vaccine induces immune responses in 50 healthy, HIV-negative volunteers. Results from this trial are now being analyzed. A larger clinical trial to further evaluate safety, immune response, and schedule is being conducted through HVTN at several domestic sites, and a phase I clinical trial with 30 healthy volunteers will also be carried out in Uganda as a collaboration between the Makerere University-Walter Reed Project, DAIDS, and the VRC. The DAIDS Adult AIDS Clinical Trials Group is also conducting a phase I clinical trial of this vaccine in HIV-infected volunteers. Finally, the VRC has initiated a phase I clinical trial of a novel adenoviral HIV multiclade vaccine. The VRC eventually plans to combine DNA and adenoviral vector technologies into a prime-boost strategy for HIV vaccine development.

The Vaccine Research Center develops vaccines for biodefense. For example, the Center is currently testing an attenuated poxvirus called MVA as a safer alternative to the current smallpox vaccine. The vaccine was provided by Therion Biologics Corporation in collaboration with the VRC. Two phase I clinical trials are now under way testing MVA in both vaccinia-naïve and vaccinia-immune populations. In addition, VRC investigators, in collaboration with the U.S. Army Medical Research Institute for Infectious Diseases and the CDC, have developed a DNA vaccine to prevent Ebola virus infection; after promising results in nonhuman primates, a candidate Ebola vaccine began human testing in November 2003. In addition, the VRC is currently conducting preclinical testing of a fast-acting candidate Ebola vaccine that protects monkeys exposed to the virus 1 month after immunization; such a vaccine would be especially useful in an acute outbreak setting. If this vaccine proves similarly effective in humans, it could one day be used to quickly contain Ebola outbreaks

with ring vaccination—the same strategy used in the past against smallpox. A second generation product may also be evaluated that would potentially provide coverage for Marburg and possibly Lassa virus.

VRC also is developing vaccines for naturally emerging infections such as West Nile virus and SARS. For West Nile, VRC scientists have adapted an existing DNA plasmid vaccine platform to express West Nile proteins; these vaccine constructs are currently undergoing immunogenicity and viral challenge studies in rabbits. And in collaboration with Vical Inc., VRC has produced a supply of the vaccine to be used in a human phase I trial scheduled for early 2005.

In response to the recent global outbreak of SARS, VRC investigators began work immediately on the development of a potential vaccine. A Cooperative Research and Development Agreement and contract were established with GenVec, Inc., which is producing preclinical and clinical grade adenoviral vectors that express several SARS proteins. The VRC is evaluating these candidates preclinically, and will continue to develop and test adenovector-based vaccine candidates against SARS that are suitable for rapid advancement toward clinical trials. In addition, the VRC has contracted with Vical to manufacture a SARS DNA-based vaccine encoding the spike (S) glycoprotein of the SARS coronavirus. Recent studies have demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model. A phase I trial of this recombinant DNA vaccine developed at the VRC is planned for early 2005.

The development of a contractor-leased and contractor-operated Vaccine Pilot Plant (VPP), which will manage production of multiple vaccine candidates originating from VRC, is a high priority. Working in concert with the Vaccine Production Laboratory located on the Bethesda, Maryland, campus, VPP will transfer new vaccine technology for pilot-scale production of vaccine material for use in clinical trials. With a projected completion date of late 2005, the VPP will have the capacity to produce four to eight clinical lots of vaccine annually.

Finally, an expanded capacity to conduct immunology assays is needed to support expanded NIAID-supported clinical trials of intramurally-generated vaccine products. To fill this need, the Immune Assessment Laboratory Service has been proposed to accelerate immunologic testing of candidate vaccines for HIV/AIDS, biodefense, and emerging or re-emerging infectious disease threats.