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.

Pneumococcal vaccine trials in Kenya and Gambia are designed to test a vaccine that prevents diseases caused by *Streptococcus pneumonia*, a leading cause of death among infants and children in these countries.

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 NIAID Dale and Betty Bumpers Vaccine Research Center (VRC) conducts research that facilitates the development of effective vaccines for human disease. The VRC's primary research focus is the development of a preventive vaccine against HIV/AIDS. In addition to its work on HIV, the VRC has expanded the scope of its activities to include research on developing effective vaccines for Ebola and other viral hemorrhagic fevers, for West Nile virus, for SARS-associated coronavirus, for influenza, and improved smallpox vaccines.

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 underway 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 has recently developed a Vaccine Immune T-cell and Antibody Laboratory, in Gaithersburg, MD. This new facility will perform validated immune assays in support of phase II/III studies and product licensure and will serve as a Good Laboratory Practices resource for centralized immunogenicity testing across different NIAID-sponsored vaccine projects.

Division of Acquired Immunodeficiency Syndrome

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the AIDS epidemic. NIAID is committed to developing a preventive HIV vaccine and toward this end, provides resources and supports basic biomedical research to better understand the relationship between HIV and the immune system, preclinical development of new vaccines, and clinical research and evaluation of novel vaccines in all phases of clinical trials. NIAID supports exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages of concept genesis and evaluation through the Innovation Grants for AIDS Vaccine Research. Other basic vaccine research and design efforts, including testing in animal models, mechanism-of-action studies, and studies of HIV immune correlates, are supported through the HIV Vaccine Research and Design Program. The Integrated Preclinical/Clinical Vaccine Development Program is a multiproject program that supports iterative product development and later stage vaccine optimization.

To help expedite the development of promising HIV/AIDS vaccines, NIAID also has several novel public-private partnerships under a program titled HIV Vaccine Design and Development Teams (HVDDT). These contracts support consortia of scientists with both ideas and product development experience, from industry and/or academia, who have identified promising vaccine concepts ready for accelerated product development. This program is built around milestone-driven contracts to encourage more rapid advancement of these important products into clinical studies. Ten such contracts have been awarded since 2000. All are moving vaccine products rapidly through production and preclinical testing. Each of the original four contractors has developed experimental HIV vaccines that have entered human clinical trials. In 2005, two new HVDDT contracts were awarded to Children's Research Institute (recombinant adeno-associated virus-based vaccines) and Chiron Corporation (alphavirus replicon-based vaccines).

As of November 2005, NIAID had supported 85 HIV vaccine trials (79 phase I, 5 phase II, 1 phase III) with 53 candidate vaccines and 16 adjuvants in over 18,000 volunteers. The majority of the NIAID HIV vaccine clinical trials are conducted through the HIV Vaccine Trials Network (HVTN). Established in 2000 by NIAID, the

HVTN is a comprehensive global network of international scientists and researchers whose mission is to develop and test preventive vaccines against HIV/AIDS. The HVTN conducts all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy. The HVTN's global capacity allows for rapid expansion as vaccine candidates enter the pipeline for testing and development, and for carrying out larger scale studies of suitable vaccines. Spanning four continents, the network includes more than 25 clinical sites in the United States, Africa, Asia, South America, and the Caribbean; an operations and statistical and data management center; and a central laboratory.

The participation of international sites and the involvement of diverse populations through partnerships with host country researchers, governments, and communities are critical components of NIAID's HIV vaccine effort. They allow for studies that examine differences in HIV diversity, genetic background, nutritional status, effects of other infections, and access to health care, all of which could prove crucial to developing an effective vaccine for use around the world. In particular, the international capacity of the network facilitates studies of various HIV subtypes that might affect only a minority of the population, but could be important to the development of a vaccine that would protect people from different circulating strains of the virus.

During the past year, the HVTN initiated or continued several phase I and II HIV vaccine studies. In particular, NIAID, in collaboration with Merck, initiated a Phase IIb "proof-of-concept" trial to evaluate the efficacy of Merck's MRKAd5 HIV-1 gag/pol/nef candidate, a weakened adenovirus-based vaccine designed to prevent infection or delay HIV disease. The trial, which will enroll 1,500 high-risk volunteers in the United States, Caribbean, and South America, is recruiting volunteers.

Expanding Global Vaccine Research

In light of the changing HIV pandemic and the relatively low incidence of HIV infection in industrialized countries, even among higher risk groups, HIV vaccine testing must in large part be carried out internationally. NIAID established the HVTN to build global capacity and infrastructure with a special focus on pursuing an international vaccine research agenda. NIAID is restructuring all of its HIV clinical trials research networks to expand upon and better coordinate its global vaccine research activities, and to increase collaboration, efficiency, and flexibility. The new structure is designed to improve research efforts by encouraging greater integration of vaccine, prevention, and treatment research and by addressing high priority research questions, particularly in resource-limited settings where AIDS is most devastating.

Collaboration and Partnerships

The AIDS Vaccine Research Working Group (AVRWG) assists the NIH in developing a comprehensive research program aimed at expediting the discovery and development of an HIV/AIDS vaccine. The members of the group provide technical assistance to NIH through their assessment of the 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, efforts to understand the mechanisms of protection in animal models, and potential new targets for vaccines.

The Vaccine Developmental Resources Group (VDRG), consisting of NIAID staff and external scientists, was established in FY 2005. This group will assist DAIDS staff in designing and reviewing protocols for the Simian Vaccine Evaluation Units to answer scientific questions

and advance the AIDS vaccine field. The VDRG will also help NIAID assess the need for government support to advance promising candidate vaccines into and through the clinical stages of testing.

A formal collaboration for HIV vaccine research, development, and testing was established in 2003 between the NIAID and the U.S. Army Medical Research and Materiel Command (USAMRMC) through an interagency agreement with the Department of Defense (DoD). This collaboration helps ensure that U.S. government HIV vaccine research is well coordinated, efficient, and comprehensive. The strategic and scientific strengths of the USAMRMC give NIAID greater access to the USAMRMC HIV/AIDS research program focused on vaccine product development. It also allows NIAID access to the extraordinary DoD medical infrastructure and extensive experience in establishing and supporting operations in developing areas. Several vaccine trials have been initiated as part of this collaboration. The most notable is a phase III study, RV144, in Thailand that began in September 2003. RV144 will evaluate an HIV vaccine strategy known as "prime-boost," which combines two different vaccines, in this case ALVAC-HIV and AIDSVAX B/E. Each vaccine induces a different arm of the immune system. This trial enrolled approximately 16,000 uninfected volunteers by the end of 2005. This collaboration has also led to the initiation of three phase I clinical trials that will evaluate the LFn p24 HIV vaccine, a multiclade HIV-1 DNA plasmid vaccine, in Uganda, and live recombinant modified vaccinia Ankara (MVA)-CMDR (HIV-1 CM235 env/CM240 gag/pol) vaccine in the United States and Thailand. In addition, a vaccine preclinical testing laboratory, utilizing standardized *in vitro* assays and animal models, has been set up at a U.S. Military HIV Research Program (USMHRP) Walter Reed Army Institute of Research site to test vaccines supported by NIAID. This laboratory will help identify assays and animal models that predict human immunogenicity and help NIAID prioritize further candidates for further development.

NIAID has also led the development of the Partnership for AIDS Vaccine Evaluation (PAVE), which plans and harmonizes clinical trials conducted under the sponsorship of the U.S. Government. The goal of PAVE is to achieve better harmony and increased operational and cost efficiencies in the conduct of HIV vaccine clinical trials with U.S. agencies and their major partners. PAVE is a voluntary consortium that is part of a global effort to share information. It pools intellectual resources and experience to achieve fundamental goals shared by a number of U.S. government agencies that can be achieved more readily through a collaborative process. Members include NIAID's VRC, DAIDS, and HVTN; the Centers for Disease Control and Prevention (CDC); and DoD's USMHRP.

Following a proposal by a group of scientists and endorsement by the G-8 and President Bush at the Sea Island Summit in June 2004, the Global HIV Vaccine Enterprise was created to foster collaboration, cooperation, and transparency in the conduct of HIV vaccine research on a global scale. The Enterprise is a voluntary consortium of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS. The overarching purpose is to efficiently bring resources to bear on gaps in HIV vaccine research, while allowing flexibility in how research is carried out. Recently, the Gates Foundation and NIAID sponsored a series of meetings in an effort to develop a strategic plan for the Global HIV Vaccine Enterprise. Their strategic plan was published online in January 2005 in the journal *Public Library of Science Medicine*.[71]

In response to recommendations by the Global HIV Vaccine Enterprise, in 2005, NIAID created a Center for HIV/AIDS Vaccine Immunology

(CHAVI). CHAVI is a virtual center that will link a large group of domestic and international scientists to elucidate the correlates of immune protection against HIV and use that knowledge to design a vaccine to elicit those specific immune responses. CHAVI will support an intensive consortium approach to address key scientific roadblocks to HIV vaccine development and to design, develop, and test novel HIV vaccine candidates, as defined by NIH and as identified by the strategic plan of the Global HIV Vaccine Enterprise. The CHAVI team is expected to be a highly collaborative, cooperative, and interactive team of leading researchers who devote the majority of their time to the application of state-of-the-art immunological tools.

Community Outreach

To help increase awareness and acceptance of clinical HIV vaccine research, NIAID works to build a working relationship with community representatives around the world. Among these efforts, community advisory boards (CABs) are essential components at all NIAID-sponsored vaccine trial sites and within the research network. CABs provide advice and perspective on whether trials are ethical and reasonable based on community concerns.

In addition, in 2001, NIAID launched the National HIV Vaccine Communications Campaign to stimulate and enhance the national dialogue concerning HIV preventive vaccines and to create a supportive environment for future vaccine studies. A steering group represents the diversity of communities affected by the AIDS pandemic and includes nationally recognized leaders in fields such as communications, the media, social marketing, community education and organizing, health care, advocacy, public policy, and HIV prevention. For more information on the HVCC, see page 10.

Future Plans

NIAID will announce awards in response to the Leadership Group and Clinical Trials Units request for applications in 2006 and 2007, respectively. In the interim, NIAID staff will continue to work with the HVTN to expand capabilities and build capacity of existing clinical trial sites. Through the USMHRP-DoD collaboration, NIAID also continues to prepare for multiple vaccine trials at sites in the United States and abroad. NIAID will also continue to work within the Global HIV Vaccine Enterprise to help ensure that the Enterprise scientific plan is implemented and to help 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 bases its priorities for vaccine research on 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), drug-resistant bacteria such as pneumococcus, and avian influenza; 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 might 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. As integral components of NIAID's 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.

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 the CDC and the Food and Drug Administration (FDA), 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, 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, supported 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 was 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 results of this study indicated that a large proportion of pneumococcal infections in children in developing countries can be prevented by pneumococcal vaccination. For more information about this trial, see *www.niaid.nih.gov/dmid/gambia*.

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 followup 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 cosponsored a study in infant macaques to examine the pharmacokinetics and tissue distribution of thimerosal (given by injection) or methyl mercury (given orally). This study compared levels of mercury in blood and brain after exposure to either thimerosal or methyl mercury. Study results were published online in *Environmental Health Perspectives* in April 2005.[72]

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 reviewed the state of knowledge about various specific immunization safety concerns and communicated its findings to healthcare providers and the public. From 2001 to 2004, the committee 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, influenza vaccine and possible neurologic complications, and vaccines and autism. Within several months of each meeting, the committee published reports of its findings and made 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—antigens that provoke an immune response—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 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's Human Immunology Centers of Excellence Program supports many mechanistic studies that will contribute to basic understandings of human immunity and responses to vaccines.

In FY 2002, the Hyperaccelerated Award/ Mechanisms in Immunomodulation Trials research program was expanded to support indepth 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 supports the HLA (human leukocyte antigen) Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (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 *http://hlaligand.ouhsc.edu*.

The Modeling Immunity for Biodefense Program was established to support development of innovative and functional mathematical models of immunity to infection, vaccines, or other therapeutic interventions with a focus on NIAID Category A, B, and C priority pathogens.

Contracts awarded under the Population Genetics and Analysis Program focus on identification of the genetic variation in human immune response genes that contribute to variations in immune responses to vaccination or infection.

The Immune Epitope Database and Analysis Program was established to develop and maintain an integrated, Web-based searchable database of antibody binding sites (B cell epitopes) and antigenic MHC-binding peptides (T cell epitopes) for a wide variety of infectious agents and immune-mediated diseases, with emphasis on Category A, B, and C bioterrorism agents, as well as emerging/re-emerging infectious diseases.

The Immune Function in Special Populations program is aimed at identifying biological mechanisms responsible for immunosuppression. It also develops protocols to enhance vaccinations and immunotherapies in immunocompromised individuals. These special populations include neonates, infants, the elderly, pregnant women, and individuals with primary immunodeficiency diseases or drug-induced immunosuppression resulting from cancer or post-transplant therapy.

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 support research on new adjuvants—additives that help stimulate human 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 that can 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 specific response characteristics; this program, which is also funded in part by the National Cancer Institute, has so far provided more than 2,300 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

The Division of Intramural Research conducts basic and applied research to develop vaccines against many infectious diseases, including pandemic influenza, malaria, pediatric respiratory diseases, SARS, hepatitis, rotaviral diarrhea, dengue, St. Louis encephalitis, and West Nile fever. Vaccine candidates for many of these diseases are currently in clinical trials. This work often involves collaborative research and development efforts that span years—or decades—before coming to fruition. For example, FluMist®, the live, attenuated, 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 NIAID.

Today, scientists in the DIR Laboratory of Infectious Diseases are among the world's foremost experts in the development of live, attenuated vaccines (LAV) such as FluMist®. LAVs are made by using specialized techniques to attenuate or weaken a virus so that it can be safely administered in a form that closely mimics natural infection. This process stimulates both local and systemic immunity, resulting in a robust immune response. At its best, a live, attenuated

vaccine gives a broader and more potent immune response than a killed vaccine formulation. LAV vaccines for measles, mumps, and rubella stimulate life-long immunity and have a long history of safety and effectiveness. However, like other types of vaccines, live vaccines have advantages and disadvantages that affect their suitability for particular applications.

For example, RSV is the most important cause of serious pediatric respiratory disease worldwide, resulting in the hospitalization of more than 100,000 infants and young children each year in the United States alone. In the 1960s, an experimental RSV vaccine made from killed virus caused a phenomenon called immune-mediated disease enhancement, which resulted in severe disease among some vaccine recipients upon natural exposure to the virus. Since then, other approaches have been pursued by RSV vaccine researchers in the DIR and elsewhere. DIR scientists and their collaborators have worked many years to develop a safe RSV vaccine, and recently developed and evaluated a recombinant LAV candidate for RSV. In a clinical trial with 1- to 2-month old infants, the vaccine was well-tolerated and stimulated an immune response that was protective against a second vaccine dose. Additional RSV vaccine candidates are in line to be evaluated clinically, and it is likely that one or more superior candidates will be identified.[73]

In 2005, efforts to develop avian influenza vaccines took on greater urgency as the deadly H5N1 avian influenza strain continued to circulate in Asia and was found in several Eastern European countries. NIAID is pursuing multiple approaches to speed the manufacture of pandemic flu vaccines, and development and evaluation of both killed and live virus vaccines is underway.

Again drawing upon their LAV expertise, DIR researchers initiated work under a cooperative research and development agreement (CRADA) with MedImmune, Inc., to develop a panel of live, attenuated avian influenza viruses with pandemic potential. Under the CRADA, DIR and MedImmune scientists will produce and test multiple vaccines against potential pandemic flu strains, starting with the H5N1 strain. In addition, DIR scientists are continuing work begun several years ago following the emergence of an H9N2 avian flu strain in Hong Kong and China that caused several human infections. A live virus vaccine developed by DIR and CDC scientists against this H9N2 avian virus has completed phase I clinical testing for safety and efficacy.

Live-attenuated vaccines for pandemic influenza may be particularly useful because they could very rapidly induce immunity in persons with no previous exposure to the virus and might be effective with a relatively small dose. An LAV could also stimulate effective immunity to a circulating pandemic virus that differs significantly from the vaccine strain, a real possibility given both the biology of influenza viruses and the lengthy flu vaccine production process. In addition, an intranasal LAV pandemic flu vaccine could be easily administered by nonmedical personnel or given as a booster to a killed vaccine.

To mitigate concerns about the possibility of a pandemic vaccine virus reassorting with a seasonal influenza virus, deployment of an intranasal LAV pandemic flu vaccine would likely have to await clear evidence that human-to-human transmission of an avian virus had reached the pandemic stage. However, pursuing multiple strategies to develop pandemic influenza vaccines increases the odds that effective weapons will be available if they are needed.

While pandemic influenza vaccines are receiving increasing attention and resources, other important DIR vaccine programs continue in earnest, particularly the malaria vaccine programs underway in DIR's Malaria Vaccine Development Branch (MVDB). The MVDB 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 MVDB has several malaria vaccine candidates in clinical trials in the United States and in malaria-endemic countries, and several more vaccine candidates in preclinical testing or under development in the laboratory. Additional information can be found in the malaria section on page 111.

Vaccine Research Center

The NIAID Vaccine Research Center is dedicated to translating basic science knowledge into clinical vaccine products. This requires the ability to do basic research, construct new vaccine products, perform preclinical research, and evaluate candidate vaccines in phase I human studies. To conduct human clinical trials, the VRC has established the infrastructure to produce vaccine products using good manufacturing practices, and to manage regulatory issues related to human trials. This includes a dedicated clinical trials staff for volunteer recruitment and clinical evaluation of approximately 300 healthy adult volunteers per year.

The VRC's prime-boost vaccine candidate, which uses a multiclade multigene DNA plasmid vector prime, adenoviral vector (ADV) boost strategy, has progressed through phase I clinical trials. The VRC has been given permission by the U.S. FDA to proceed with a phase II trial. The two vaccines (6-plasmid DNA and 4-vector ADV) developed by the VRC incorporate HIV genetic material from clades A, B, and C, which cause about 90 percent of all HIV infections around the world. These are the first multigene, multiclade HIV vaccines to reach clinical phase II, marking an important milestone in the search for a single vaccine strategy that targets U.S. subtypes of HIV as well as clades causing the global epidemic. In phase I studies of the separate components, the vaccines were shown to be well tolerated and elicited cellular and humoral responses. A recently launched trio of trials of this prime-boost strategy, sponsored by DAIDS and to be conducted by three international networks, the HVTN, the International AIDS Vaccine Initiative, and USMHRP, will test the safety and immunogenicity of the prime-boost strategy in the Americas, Southern Africa, and Eastern Africa.

The VRC also develops vaccines for biodefense. For example:

- Investigators at the VRC, with scientific collaborators at the U.S. Army Medical Research Institute for Infectious Diseases, and the CDC, have developed a potentially effective vaccine strategy for Ebola virus infection in nonhuman primates. In November 2003, the VRC initiated the first human clinical trial of a DNA vaccine designed to prevent Ebola infection. The vaccine was well tolerated at all dose levels, and there is evidence of both humoral and cellular immune responses at all doses. Final data analysis is currently in progress.

- The VRC plans to evaluate a fast-acting, recombinant adenoviral vector (rAd) Ebola vaccine. Such a vaccine would be especially useful in an acute outbreak setting. If this vaccine proves to be effective in humans, it could one day be used to quickly contain Ebola outbreaks with the same ring vaccination strategy used in the past against smallpox. This product is currently in the preclinical testing phase, and a phase I study is projected to begin midyear 2006.

- Preclinical development work is evaluating another Ebola preventive regimen that could include either a rAd Ebola vaccine alone, or a DNA prime-rAd Ebola vaccine boost approach.

- The VRC is currently testing MVA as an attenuated poxvirus with the potential to protect against vaccinia (the virus used to vaccinate against smallpox) or variola (the virus that causes smallpox). The vaccine was provided by Therion Biologics Corporation as part of a collaboration with the VRC. Two phase I clinical trials testing MVA as a component of a safer smallpox vaccine in both vaccinia-naïve and vaccinia-immune populations were recently completed.

The VRC is developing vaccines for naturally emerging infections such as West Nile virus and SARS. For West Nile, in April 2005, following preclinical safety studies and viral challenge studies, the VRC initiated a phase I clinical trial to evaluate safety, tolerability, and immune responses of a candidate recombinant DNA vaccine in human volunteers. In response to the recent global outbreak of SARS, VRC investigators began work immediately on the development of a potential vaccine. A CRADA and contract were established with GenVec, Inc., to produce preclinical and clinical grade adenoviral vectors that express several SARS proteins. The NIAID Vaccine Research Center plans to evaluate the immunogenicity of these vectors 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, Inc., 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 was initiated in mid-December, 2004.

Finally, VRC is constructing a contractor-leased and -operated Vaccine Pilot Plant (VPP), which will manage production of multiple vaccine candidates originating from VRC. To achieve this high priority objective, VPP will coordinate with the Vaccine Production Laboratory located at the NIH campus in Bethesda, Maryland, to transfer new vaccine technology for pilot-scale production of vaccine material for use in clinical trials. The VPP will be a self-contained facility of 126,900 square feet with the capacity to produce four to eight clinical lots of vaccine annually.