OFFICE OF THE DIRECTOR

The Office of the Director (OD), NIAID, provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the focal point of relationships with the Director of the NIH as well as with other components of the Department of Health and Human Services (DHHS), other Federal agencies, Congress, professional societies, voluntary health organizations, and other public groups. The activities of OD also include advising and guiding NIAID's key leaders on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs. Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, OD offices play a key role in helping the Institute achieve its mission. Brief descriptions of OD offices follow.

The Office of Administrative Services (OAS) assists NIAID staff members in carrying out their responsibilities by providing administrative and acquisition management support services. These services include procurement, space management, and travel. OAS also develops internal controls in areas such as property accountability and financial monitoring, and coordinates and analyzes organizational changes.

The Office of Clinical Research manages and coordinates the NIAID research programs conducted at the Warren Grant Magnuson Clinical Center located on the NIH Bethesda campus. The Office promotes interactions and collaborations between intramural and extramural investigators and oversees NIAID's Institutional Review Board to provide initial and continuing review of intramural clinical research protocols to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. The Office also provides relevant information from NIAID's intramural clinical research programs to the NIH community and other Government agencies, as well as to public and private organizations.

The Office of Communications and Public Liaison (OCPL) enables NIAID to meet an important part of its mission by conveying the goals and results of its research programs to health professionals, the news media, and the public. In addition to responding to more than 10,000 requests for information annually, the Office plans educational and media campaigns; develops and disseminates brochures, fact sheets, news releases, and audiovisual products; and produces educational exhibits for national and regional meetings. OCPL also coordinates NIAID's Web site activities.

The Office of Equal Employment Opportunity is responsible for planning, implementing, evaluating, and monitoring programs and initiatives to increase the number of minorities, women, and persons with disabilities in all scientific and administrative areas of the Institute. The Office also develops initiatives that further enhance biomedical research programs at historically black colleges and universities and at Hispanic-serving institutions, and coordinates all activities to implement NIH minority-assistance programs and objectives relevant to the mission of NIAID.

The Office of Ethics provides advice regarding conflict of interest of individuals involved in the conduct of biomedical research, including Government employees, advisory committee members, and non-government employees such as peer reviewers and Data Safety Monitoring Board members. The Office also administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public.

The Office of Financial Management provides overall financial planning, management, and budget analysis to the Institute Director and all NIAID components and provides budget-related

materials for the NIAID Director's briefings with DHHS, the NIH Director, the Office of Management and Budget, and Congress.

The Office of Global Affairs (OGA) provides overall coordination of NIAID international activities through a matrix of international liaisons; it accomplishes its work with other NIH components and DHHS agencies through the Fogarty International Center. OGA also meets and greets international visitors and delegations, coordinates NIAID participation in bilateral and multilateral programs, negotiates and provides administrative support for the long-term assignment of NIAID staff and representatives overseas, and supervises the OGA/NIAID Epidemiology Group in support of intramural and extramural international projects.

The Human Resources Operations Branch C (NIAID), Division of Human Resources Operations, Office of Human Resources, NIH, provides human resource services for the Institute management, employees, and applicants. These services encompass recruitment and staffing, position management and classification, pay and compensation, employee relations, employee benefits, employee development, and advisory services.

The Office of Management for New Initiatives (OMNI) is responsible for managing the establishment of key resources for new NIAID scientific and administrative initiatives. OMNI also is charged with acquiring and developing physical, human, and contractual infrastructure to fulfill new and expanded NIAID mission requirements.

The Office of Policy Analysis provides support and serves as liaison to program managers to coordinate, integrate, and articulate long-range program goals and strategies; develop and coordinate the Institute's annual planning and reporting process; advise on material for all stages related to congressional budget presentations; direct and coordinate the legislative liaison, tracking, and analysis for the Institute; manage the Executive Secretariat function; direct and coordinate Freedom of Information Act activities; provide the secretariat function for selected advisory groups, such as the NIAID Executive Committee; prepare the NIAID Director for meetings with various constituency groups; and brief the NIAID Director in preparation for trans-NIH policy meetings.

The Office of Technology Development (OTD) supports NIAID's intramural and extramural research programs by facilitating collaborations between NIAID researchers and external research and development organizations. OTD's staff uses scientific, legal, and business expertise to negotiate agreements with universities, small biotechnology companies, large national and multinational pharmaceutical concerns, and other government institutions. OTD manages NIAID's portfolio of patents and inventions and serves as NIAID's resource for all issues concerning intellectual property. OTD also manages the receipt of Cooperative Research and Development Agreement funds, supports the NIH's licensing program, and tracks license royalty receipts. In addition, OTD provides NIAID investigators with training on NIH technology transfer policies and regulations and guidance on conflict-of-interest issues.

The Office of Technology Information Systems (OTIS) manages technologies supporting NIAID biomedical research programs. The Office provides technology management and development; engineering for scientific, information, and administrative applications; bioinformatics support and coordination; and specialized professional development activities. OTIS works with intramural, extramural, and administrative staff within NIAID and with collaborative programs of the Institute. Activities include policy and technological support, liaison and coordination, and consultation. Program initiatives and projects ensure effective management and broadened and intensified use of technologies to serve NIAID strategic biomedical goals, nationally and worldwide.

OUTREACH ACTIVITIES

The NIAID Office of Communications and Public Liaison (OCPL) is the focal point within the Institute for disseminating research results to the media, health professionals, and the public. An important part of NIAID's mission, this activity includes producing and disseminating print, audiovisual, and Web-based materials; distributing materials at professional and community meetings; and sponsoring workshops and conferences for community healthcare providers and the general public. Other NIAID divisions and offices also initiate and participate in targeted outreach actitivies.

OCPL produces materials on topics ranging from allergic and immunologic diseases, to AIDS and other sexually transmitted infections, to potential illnesses caused by agents of bioterrorism. These materials include press releases, information sheets, and booklets, which are distributed to more than 10,000 people who contact the Institute from around the world each year. In addition, hundreds of thousands more download or request materials from the NIAID Web site (*www.niaid.nih.gov*), which is now visited approximately 800,000 times each month.

The NIAID Web site is a searchable site containing a wealth of information about NIAID's organization and research programs, as well as descriptions of NIAID's laboratories. The Extramural Information Center includes program announcements, contact information for key personnel, and many other items of interest to current and potential grantees and contractors.

OCPL has updated and printed its award-winning booklet on allergy—*Airborne Allergens: Something in the Air*—and published a new booklet called *Food Allergy: An Overview.* In addition, OCPL has updated and printed three very popular booklets: *Lyme Disease: The Facts, the Challenges; Understanding Vaccines: What They Are, How They Work;* and *Understanding the Immune System: How It Works.* OCPL distributed thousands of copies of the previous editions of these booklets to lay public, healthcare providers, research institutions, and researchers around the world. All publications are also available on the NIAID Web site.

Exhibiting at scientific and health-related meetings is a key element of OCPL's outreach efforts. Institute staff distribute materials and answer questions about NIAID research and job opportunities at conferences, including those sponsored by the American Academy of Allergy, Asthma and Immunology; the American Society for Microbiology; the Infectious Diseases Society of America; the Hispanic Association of Colleges and Universities; the American Public Health Association; and the Congressional Black Caucus.

An OCPL communications initiative continues to expand NIAID's efforts to keep hundreds of voluntary and scientific organizations updated about Institute activities. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of the organizations. In addition, OCPL disseminates news from NIAID through the *NIH Public Bulletin*.

OCPL recently has become involved in outreach activities related to the construction of several NIAID-funded biosafety laboratories. Most prominent among these activities is the neighbor outreach program in Hamilton, Montana, where a new Integrated Research Facility is planned for construction at NIAID's Rocky Mountain Laboratories (RML). A database of RML neighbors has been established so RML can communicate with them rapidly regarding issues related to ongoing activities and new construction at RML. In addition, RML has established a Community Liaison Group that meets regularly and receives updates about plans for development on the RML campus.

In addition, RML recently sponsored two informational symposiums for the community. The symposia combined the talents of local health experts and research scientists from NIAID in Bethesda, who shared the stage in presenting information to the community and answering their questions. The symposium on West Nile virus infection drew approximately 200 community members, including the governor of Montana.

The second symposium on pandemic influenza was attended by approximately 100 community members. RML also collaborated with the State public health agency to share a video of the symposium with more than 50 county and tribal health offices. A DVD of the influenza symposium was sent to the Montana Department of Public Health and Human Services to circulate to about 50 of their health jurisdictions.

RML also presents educational programs for children in three of the local middle schools in the area. The program is called the "Biomedical Research After School Scholars," or BRASS, program. Most recently, five different classes were given on different topics in biomedical research, such as cell biology and immunology, to seventh and eighth graders.

OCPL has been involved in the outreach efforts of NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC) as well. The VRC is the first facility at NIH dedicated solely to vaccine research and production. To help the Center with its recruiting efforts for HIV vaccine trials, including the recruitment of underrepresented groups of volunteers, OCPL is proposing volunteer stories to local news media, helping to develop recruitment ads, and coordinating the development of informational materials that can be used by both the VRC and the NIAID-supported extramural HIV Vaccine Trials Network.

NIAID's Division of AIDS is conducting a national HIV Vaccine Communications Campaign (HVCC) to create a supportive environment for HIV vaccine research. The campaign is designed to create a dialogue to help the public better understand the research, support it, and support those who volunteer for clinical trials. The Institute implemented a qualitative comprehensive research effort, including both primary research (for example, 28 focus groups representing communities most affected by HIV/AIDS) and secondary, or existing, research.

A national survey was conducted in which the attitudes and knowledge about HIV vaccine research were evaluated in the general population as well as in segmented groups of African-Americans, Hispanics/Latinos, and men who have sex with men (MSM). Results of the survey show that misinformation and distrust continue to present formidable barriers to support for HIV vaccine research and that low public awareness and knowledge of HIV vaccine research must be addressed to develop and sustain HIV vaccine clinical research efforts. NIAID staff used the research findings to identify key messages and formulate a campaign strategy that would be both effective and powerful. The HVCC key messages include 1) currently there is no HIV preventive vaccine; 2) only HIV-negative individuals may participate in HIV preventive vaccine trials; 3) a person cannot get HIV from the vaccines being tested; 4) in order for us to develop an HIV vaccine that works for all populations, all populations must participate in clinical trials; and 5) HIV vaccines are our best hope to end the HIV pandemic.

Another major activity of the HVCC is to coordinate activities for the annual HIV Vaccine Awareness Day (HVAD) on May 18th. HVAD was established as a day to acknowledge and thank all the volunteers and researchers involved in HIV vaccine research. Community activities and media events around the country highlight research advances, address challenges associated

with HIV/AIDS, and recognize volunteers who have participated in HIV vaccine clinical trials.

The HVCC also sponsors the Community Education and Outreach Partnership Program (CEOPP). This program was designed to create local and national partnerships aimed at increasing the campaign's ability to provide messages to high-risk populations, specifically African Americans, Hispanics/Latinos, and MSM; ensure the inclusion of HIV vaccine research information in prevention, care, and treatment programs/curricula/literature; eliminate myths, misconceptions, misperceptions, and misinformation relating to HIV prevention vaccine research; and measure the effectiveness of campaign messages. In 2004, 8 national and 20 community organizations were awarded CEOPP subcontracts.

RESEARCH PLANNING

NIAID has a long-standing tradition of rigorous and prospective research planning, involving the development and prioritization of specific research initiatives on an annual basis and long-range strategic planning. NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health.* The two pillars of this research planning process are the annual Winter Program Review (WPR) and the Summer Policy Retreat (SPR).

Program Reviews

NIAID's annual program reviews provide an opportunity to focus on future research opportunities and to review proposed research initiatives for new and ongoing research programs.

The specific objectives of the annual program reviews are to:

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Discuss the scientific framework for and priority of new and ongoing research programs in the context of the above factors; and
- Use this information to make decisions about research activities and initiatives to be implemented in the future budget year.

Policy Retreats

The planning process is further enriched through annual policy retreats that provide opportunities to:

- Focus on broad scientific issues, opportunities, gaps, and directions;
- Identify the basis for scientific opportunities and gaps;
- Ensure that scientific planning addresses the interests and priorities of the Congress, the Administration, the Department of Health and Human Services (DHHS), and the NIH Director;
- Propose approaches for responding to newly identified opportunities and needs;
- Identify the implications of changes in scientific or programmatic direction; and
- Prioritize newly identified opportunities and needs within the future budget year.

Throughout the year, NIAID convenes scientific workshops, blue ribbon panels, and program reviews to evaluate progress and to determine future needs and opportunities for the many diseases and areas of research within the Institute's purview. The NIAID Director and each research division consult extensively with NIAID stakeholders, including scientific experts, professional societies, and patient advocacy groups, to develop long-range strategic plans as well as specific research initiatives. Areas of emphasis articulated in strategic plans, as well as those identified by DHHS, the NIH, Congress, the White House, and others, also help shape the Institute's decision-making and priority-setting process for new and continuing research programs.

Planning for future research initiatives is a multistep process that begins 2 years in advance of the projected implementation date. At each step in the process, the concepts for research initiatives are reviewed and refined. Concepts are first subjected to internal discussion during the annual program review, followed by a second level of review and clearance by the National Advisory Allergy and Infectious Diseases Council. Approved concepts are then developed by NIAID staff into various forms of grant and

contract solicitations and announced to the scientific community. Proposed research projects are then peer-reviewed and awarded on the basis of scientific merit, program relevance, and need.

Strategic Planning

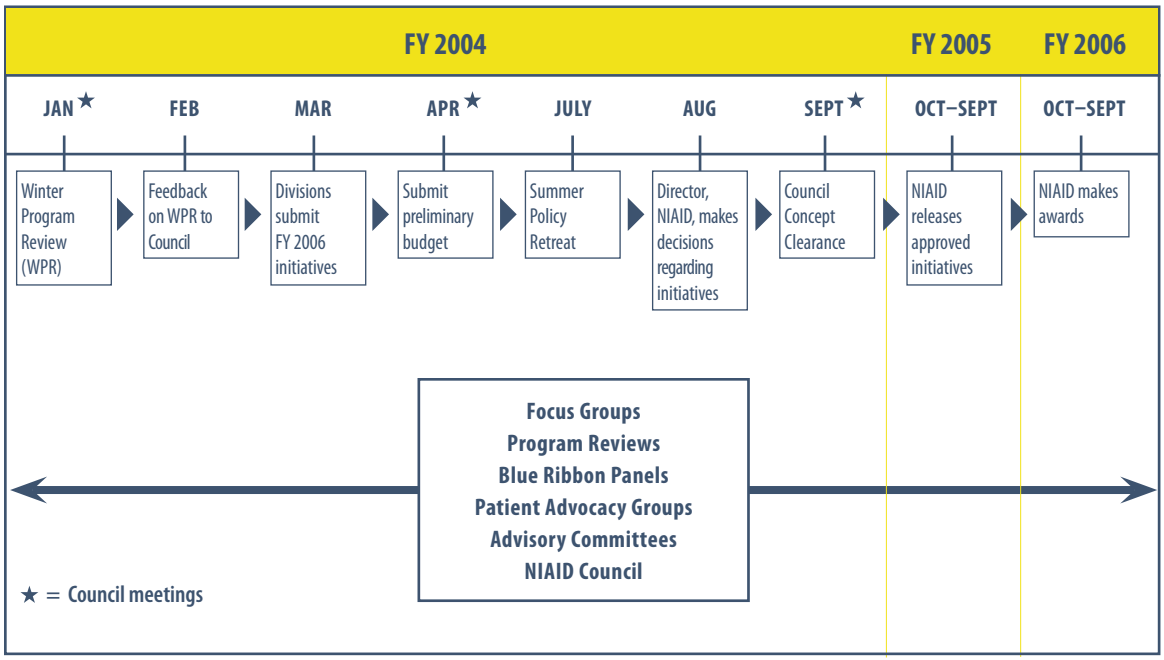
NIAID's comprehensive strategic plan, *NIAID: Planning for the 21st Century,* is the product of an intensive effort that included a task force of national experts. The plan describes broad-based priorities to guide NIAID programs, policies, and initiatives through the next 3 to 5 years. The cornerstones of the plan are (1) immune-mediated diseases, (2) human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), (3) emerging infectious diseases and global health, and (4) vaccines. The full text of the plan can be accessed at *www.niaid.nih.gov/strategicplan.*

The Institute's guiding principles for global health research are articulated in the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis.* This plan identifies short-term, intermediate, and long-term research goals to address these devastating international killers. The plan can be accessed at *www.niaid.nih.gov/publications/globalplan.htm.*

Since the anthrax mail attacks of 2001, biodefense research has become a major component of NIAID's mission. The vigorous growth of the NIAID biodefense program is guided by expert recommendations and an intricate strategic planning process. In 2002, NIAID convened the first Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research to assist in developing the *NIAID Strategic Plan for Biodefense Research,* the *NIAID Biodefense Research Agenda for CDC Category A Agents,* and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens.* The strategic plan emphasizes basic research on microbes; host defense mechanisms; and the development of drugs, vaccines, and diagnostics. The biodefense research agendas articulate immediate and longer term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, Rift Valley fever, and Lassa virus; and goals for research on Category B and C priority pathogens. The agendas also address the research resources, facilities, and scientific manpower needed to conduct basic and applied research on these potential agents of bioterrorism. Both the strategic plan and the research agendas can be accessed at *www.niaid.nih.gov/publications/bioterrorism.htm.* Tremendous progress has been made since these reports were first released. NIAID has increased the breadth and depth of biodefense research and has made progress in meeting the specific goals of the Blue Ribbon Panel. The *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report* describes the progress made toward addressing the immediate goals outlined in the research agenda and can be accessed at *www2.niaid.nih.gov/biodefense/research/category_a_Progress_Report.pdf.*

Another important strategic planning effort focuses on how to further stimulate research activities to address health disparities. The NIAID *Strategic Plan for Addressing Health Disparities* articulates specific action plans for reducing disparities through (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases; (2) support for research infrastructure and research training; and (3) support for community outreach projects. The full text of the health disparities strategic plan can be accessed at *www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.*

NIAID PRIORITY-SETTING PROCESS



DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) was established in 1986 to help end the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus (HIV), supporting the development of therapies for HIV infection and its complications and co-infections, and supporting the development of vaccines and other prevention strategies. To accomplish this, DAIDS plans, implements, manages, and evaluates programs in fundamental basic research; discovery and development of therapies and treatment strategies for HIV infection; its complications and co-infections; and discovery and development of vaccines, topical microbicides, and other prevention strategies. Staffed by over 120 employees, DAIDS is comprised of three main scientific programs—the Basic Sciences Program, the Vaccine and Prevention Research Program, and the Therapeutics Research Program.

Scientific Areas of Focus

Basic Research

HIV pathogenesis research increases our understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. HIV pathogenesis research also supports studies of how the immune system responds to the virus. Epidemiologic and natural history research provide information about HIV biology and clinical course of HIV in human populations, which enhances understandings of risk factors for HIV transmission and development and progression of HIV disease. Knowledge gained from these studies enhances researchers' abilities to create new agents and vaccines to combat HIV infection.

DAIDS is studying the natural history of HIV progression in men and women through its cohort studies. The Women's Interagency HIV Study (WIHS) is a collaborative, multisite longitudinal study designed to investigate the impact of HIV infection on women in the United States (*http://statepiaps.jhsph.edu/wihs*). The Multicenter AIDS Cohort Study (MACS) is an ongoing study of the natural history of HIV infection in homosexual men (*http://statepi.jhsph.edu/macs/macs.html*). MACS began in 1983 and was able to capture information about a large number of men who seroconverted while enrolled in the study. The Women and Infants Transmission Study (WITS) examines the natural history of HIV disease in the context of pregnancy, focusing on clinical, laboratory, and psychosocial aspects of maternal/infant transmission. WITS currently is investigating the long-term consequences of exposure to HIV and antiretrovirals in the children born during the study. Programs that study men and women separately give researchers the ability to make gender-based comparisons, thereby adding value to the analyses.

DAIDS also supports a large portfolio of investigator-initiated grants in HIV pathogenesis in a variety of areas, including mechanisms of viral entry and infection; structure, function, and mechanism of action of viral genes and proteins; roles of cellular accessory molecules in replication; immunologic and virologic events controlling primary infection and formation of latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression. These grants serve as a source of new knowledge that fuels the discovery of new drugs and vaccine concepts.

To further stimulate the pursuit of new ideas, DAIDS funds a number of targeted programs, such as the Innovation Grants for AIDS

Research Program, which provides limited funds for 2 years to help advance novel ideas that lack extensive preliminary data. The Novel HIV Therapies: Integrated Preclinical/Clinical Program is another example of how DAIDS supports the discovery, development, and evaluation of innovative HIV treatment concepts through multidisciplinary research and formal corporate partnering. The Centers for AIDS Research program, also supported by DAIDS, provides administrative and resource support and emphasizes the importance of translational research and collaborations between basic and clinical investigators.

To assist the research community, NIAID supports the NIH AIDS Research and Reference Reagent Program, which is now in its 16th year of operation. The Reagent Program continues to provide the scientific community worldwide with a critical and unique resource for biologics and chemicals.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, DAIDS-funded investigators have identified the critical steps of how HIV uses the host machinery to enter and exit the cell, as well as the existence of multiple, persistent HIV reservoirs even with the use of highly active antiretroviral therapy (HAART). Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication and about why the host immune response is not fully effective in controlling the infection. Information about how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

Therapeutics

In order to foster development of new HIV therapies, DAIDS supports research on potential new cellular and viral therapeutic targets, as well as new approaches to validate targets. The areas of research include identifying molecules that could effectively block HIV replication, improved formulations of existing agents, approaches to restore the immune system of HIV-infected individuals, molecular and genetic approaches to protect susceptible uninfected cells, combination regimens that impede the emergence of viral resistance, and assays to measure restored immunity of HIV-infected individuals. Clinical studies help determine which new agents are effective against HIV and its associated complications and co-infections, and also clarify how best to use these drugs. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics, and advanced clinical testing in humans.

The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. Clinical studies define new agents that are effective against HIV and its associated opportunistic infections and co-infections and clarify how best to use these drugs. DAIDS supports clinical therapeutic research in adults and children through several large clinical trials networks, including the Adult AIDS Clinical Trials Group (*http://aactg.s-3.com*), the Pediatric AIDS Clinical Trials Group (*http://pactg.s-3.com*), the Terry Beirn Community Programs for Clinical Research on AIDS (*www.cpcra.org*), and the Acute Infection and Early Disease Research Program (*http://www.aiedrp.org*).

DAIDS-sponsored therapeutics research already has had a dramatic impact on our understanding of the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped to define national and international guidelines for the treatment of primary HIV infection and associated opportunistic infections and co-infections, as well as prophylactic regimens for these secondary infections; (2) identified

biological markers such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression; and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-child transmission (MTCT) of HIV.

More recent studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and ways to rebuild and replace immunity lost to HIV infection. In addition, DAIDS is developing strategies to address critical questions regarding the long-term effects of antiretroviral therapy and the most optimal approaches to medical management, especially to prevent MTCT.

Vaccine and Prevention Research

The discovery and development of an HIV/AIDS vaccine for the prevention of HIV infection and AIDS is a high priority of the NIAID. Through a balanced HIV program that integrates both basic research and empiric testing of candidate vaccines, NIAID supports a broad spectrum of research and development on HIV/AIDS vaccines. Preclinical vaccine research and development examines new vaccine concepts or approaches and new ways to deliver HIV antigens to people and to safely induce a potent anti-HIV immune response. Studies in animal models are aimed at defining how a vaccine could protect the host.

Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) (*www.hvtn.org*). HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. Started in 2000, it has made progress towards its goal of developing and conducting a comprehensive HIV vaccine clinical research agenda that addresses scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. HVTN has undergone significant expansion to support international trials, instituted highly functioning protocol development teams, developed new vaccine concepts and advanced new protocols, reorganized laboratory programs, and developed an extensive training program. (Additional HVTN information is located in the Vaccine Research and Development section of Selected Scientific Areas of Research on page 127.)

Vaccine research and development are supported through an extensive portfolio of investigator-initiated research in basic virology, immunology, and microbiology. Several DAIDS programs support the interface of preclinical and clinical research. These resources stimulate the development of new vaccine concepts and ensure a rational, deliberate process for moving concepts through to clinical trials. Among the vaccine research programs supported by DAIDS that encourage development along various stages of the vaccine pipeline are the Innovation Grants for Approaches in HIV Vaccine Research Program, which encourages novel and innovative concepts in vaccine discovery and development; the HIV Vaccine Research and Design Program, which supports concepts that have evolved beyond early testing and "matured" innovation grants; and the Integrated Preclinical/Clinical AIDS Vaccine Development Program, which supports the iterative processes of vaccine concept refinement and testing. Through this program, research groups investigate promising vaccine concepts

that are amenable to product development and are likely to lead to preliminary studies in humans. In addition, HIV Vaccine Design and Development Teams, consisting of consortia of scientists from industry and/or academia, identify specific promising vaccine concepts amenable to targeted development.

NIAID also supports comprehensive research on other biomedical/behavioral prevention approaches, including the prevention of MTCT of HIV, topical microbicides, interventions that reduce behaviors that expose people to HIV, programs to reduce intravenous drug abuse, measures to control other sexually transmitted diseases (STDs), and antiretroviral therapies that may reduce the spread of HIV from infected people to their partners.

Non-vaccine HIV prevention research is conducted primarily through the HIV Prevention Trials Network (HPTN) (*www.scharp.org/hptn*). The HPTN, formed in 2000 with additional support from the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, is a global, multicenter network dedicated to nonvaccine prevention research. Additional HPTN information is located in the AIDS section on page 41.

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. In the past, NIAID-supported researchers have improved the ability of vaccines to induce an antibody response by modifying the envelope protein, further explained the envelope structure of HIV, advanced understandings of the role of cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes, developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies will address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. In other prevention research, new microbicides will be evaluated for their safety, acceptability, and ability to prevent the sexual transmission of HIV. Moreover, building on past research that identified an inexpensive regimen to reduce HIV transmission at birth, NIAID will continue to evaluate other practical regimens for preventing MTCT of HIV, especially during breastfeeding.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's prevention and treatment research activities are conducted on a global scale. In fiscal year 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda relevant to their populations and to strengthen the infrastructure required to carry out this research. As their national research capacity grows, countries can seek renewable CIPRA funding for multidisciplinary research projects and/or clinical trials for HIV prevention and/or treatment. For more information, visit the Web site at *www.niaid.nih.gov/daids/cipra*.

Advisory Groups

DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with a number of advisory groups and community and health professional organizations to help evaluate and redirect the Division's global research programs by identifying research needs, setting priorities, and planning future programs. These advisory bodies include the AIDS Research Advisory Committee (ARAC) and the AIDS Vaccine

Research Working Group (AVRWG). The ARAC advises the Directors of DAIDS and NIAID on all aspects of the research portfolio, reviews progress and productivity of ongoing efforts, provides assistance in identifying critical gaps/obstacles to progress, and approves of concepts for new initiatives. The AVRWG assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine.

Collaborations

DAIDS actively supports and promotes public and private-sector alliances to maximize available research opportunities and resources. Our commitment to identify effective prevention strategies and treatments has led to a steady increase in international activities, particularly in the developing world, where there is critical need for cost-effective prevention, treatment, and care. These efforts, in particular, necessitate collaboration with other Federal and non-Federal agencies, given the complexity of global research efforts. As a result, NIAID has forged collaborations with the Centers for Disease Control and Prevention (CDC) and Department of Defense (DoD) in order to bring together the vast expertise, experience, and resources of each organization and help foster coordination and efficiency. The Partnership for AIDS Vaccine Evaluation (PAVE) is one example of collaboration between NIAID, CDC, and DoD that was established as a way to accelerate global HIV vaccine research efforts and increase efficiency and cost effectiveness through shared laboratory capabilities, clinical trial sites, and compatibility of protocols and data.

Domestic and International Activities

With the growing global impact of HIV/AIDS, there is a critical need for cost-effective prevention and treatment strategies in limited-resource regions of the world where more than 95 percent of HIV infections occur. With the explosive growth of new infections in the developing world, most of DAIDS-funded clinical research programs now have an international component. DAIDS supports research at academic and medical research centers, and collaborates with research and development companies worldwide. Many of DAIDS' activities support countries listed in the President's Emergency Plan for HIV/AIDS Relief (PEPFAR), which include Cote d'Ivoire, Botswana, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. While domestic research continues to focus on identifying the most effective treatment and prevention options for adults, adolescents, and children, internationally-focused activities are designed to define global research priorities, ensure the clinical relevance of future vaccine and prevention strategies to human populations most in need, strengthen collaborations with local investigators worldwide, and support training and infrastructure development in developing countries.

Role of Community

DAIDS has long recognized the importance of sustained relationships with the community, which are necessary to help foster and maintain trust and ensure that the research is designed to meet community needs. Each of the clinical research networks supported by DAIDS has a Community Advisory Board (CAB) that works with the leadership of the network on all aspects of the research process, and other CABs that work with each individual research site. The CABs help ensure that the researchers are working in partnership with the community and help to improve communications to the community and from the community to researchers. Community outreach and education are also integral components of the Division's activities.

Major programs supported by DAIDS

- Acute Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- HIV Prevention Trials Network
- HIV Vaccine Design and Development Teams
- HIV Vaccine Research and Design Program
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Trials Network
- Innovation Grant Program
- HIV Vaccine Communications Campaign
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Integrated Preclinical/Clinical AIDS Vaccine Development Program
- Multicenter AIDS Cohort Study
- Pediatric AIDS Clinical Trials Group
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Women and Infants Transmission Study
- Women's Interagency HIV Study

DIVISION OF ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION

Mission

The human immune system is composed of intricate networks of specialized cells, molecules, and organs that act together to defend the body against foreign invaders such as viruses, bacteria, and fungi that may cause disease. However, aberrant immune responses play a critical role in the development of immune-mediated diseases, which include asthma and allergic diseases; autoimmune disorders; primary immunodeficiencies; and rejection of transplanted solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

The past two decades of focused research on the immune system have resulted in major advances in understanding the mechanisms that underlie a range of immune-mediated diseases. These advances in conceptual understanding now provide realistic opportunities for improvement in the diagnosis, treatment, and prevention of many of these diseases. The Division of Allergy, Immunology, and Transplantation (DAIT) (*www.niaid.nih.gov/research/dait.htm*) promotes and supports a broad range of research that seeks to further our understanding of the immune mechanisms underlying immune-mediated diseases and to translate this basic knowledge to clinical applications that will benefit individuals affected by these diseases. The ultimate goal of DAIT's research program is the development of effective approaches for the treatment and prevention of immune-mediated diseases.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT supports basic, preclinical, and clinical research to enhance our understanding of the causes of immune-mediated diseases and to apply this knowledge to the development of improved approaches to disease diagnosis, treatment, and prevention through demonstration and education research projects. DAIT also supports research that evaluates the effectiveness of behavioral and educational interventions to promote health and prevent disease in defined populations.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further our understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

Scientific Areas of Focus

Asthma and Allergic Diseases

Asthma and allergic diseases are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved

in these disorders and on approaches to improve diagnosis and treatment by fostering investigator-initiated projects and supporting cooperative clinical studies. The Inner-City Asthma Consortium (ICAC): Immunologic Approaches to Reduce Asthma Severity, a network of basic scientists and clinical investigators, was established by DAIT in fiscal year (FY) 2002 to evaluate the efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. In FY 2004, the ICAC launched a cockroach allergen standardization protocol; a study to evaluate the usefulness of measurements of exhaled nitric oxide in the clinical management of asthma in children; and a birth cohort to investigate the allergic and environmental factors that contribute to the development of asthma in inner-city children.

Autoimmune Diseases

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the United States population and disproportionately afflict women. DAIT supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease. DAIT supports the Autoimmunity Centers of Excellence, which conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies and mechanism-of-action studies. DAIT also supports the Centers for Autoimmune Disease Prevention, which focuses on advancing knowledge for the prevention of rheumatoid arthritis and other autoimmune diseases. The goal of the Autoimmunity Prevention Centers is to develop the knowledge base necessary to design preventive interventions that could be administered efficiently and safely. In FY 2004, the Prevention Centers supported 16 pilot projects to test innovative approaches that might lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression.

Basic and Clinical Immunology

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including the basic biology of immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on immune-mediated diseases, including autoimmune diseases, asthma and allergic diseases, acute and chronic transplant rejection, and immunodeficiencies. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune diseases, and methods of immune intervention.

Immune Tolerance

Immune tolerance is a high priority for NIAID, and, as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN). The ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases, asthma and allergic diseases, and rejection of

transplanted organs, tissues, and cells. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The ITN has established a variety of state-of-the-art core facilities and has supported 18 approved clinical protocols and several additional studies of the immune mechanisms that lead to development, maintenance, or loss of clinical tolerance. Currently, the ITN supports seven clinical trials in solid organ and islet transplantation and two cohort studies to better understand the immune mechanisms involved in the acquisition of spontaneous tolerance to organ grafts. More information about the ITN is available on its Web site at *www.immunetolerance.org*.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases (PIDs) are caused by intrinsic defects in the cells of the immune system and are often due to inherited genetic defects. NIAID-supported research in these diseases focuses on understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases. This includes identifying pathogenic gene mutations and other contributing etiologies and expanding the genetics knowledge base to improve diagnosis, facilitate genetic counseling and decisionmaking for affected individuals, and provide protective and curative treatments, including gene therapy. In FY 2003, NIAID, with cosponsorship from NICHD, established the Primary Immunodeficiency Diseases Consortium. The Consortium: (1) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; and solicits, reviews, and makes awards for pilot or small research projects; (2) maintains a primary immunodeficiency diseases registry, which provides data to the research community about the clinical characteristics and prevalence of these diseases; and (3) develops a repository of specimens from subjects with primary immunodeficiency diseases. Additional information on Consortium activities is available on its Web site: *www.USIDNet.org*. NIAID also supports research in large animal models of primary immunodeficiency diseases, as well as clinical trials to determine the most efficacious bone marrow transplantation regimens in patients with these diseases.

Transplantation

The Division's research in transplantation immunobiology is focused on understanding the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; developing preclinical models to evaluate promising therapies to prevent and treat graft rejection; conducting clinical trials of new therapeutic agents and approaches to improve graft survival and function; and understanding the pathogenesis of chronic graft failure and developing new treatments and preventive strategies. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trial in Pediatric Kidney Transplantation. In FY 2004, NIAID, in collaboration with other NIH Institutes, established the Clinical Trials in Organ Transplantation Consortium to improve the success of organ transplants for end-stage organ disease. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes and responses to post-transplant therapy; develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and test the safety and effectiveness of new, less toxic immunosuppressive drugs.

Primary Research Areas

Asthma and Allergic Diseases

- Asthma and Allergic Diseases Research Centers
- Inner-City Asthma Consortium
- Immune System Development and the Genesis of Asthma

Autoimmune Diseases

- Autoimmune Diseases Prevention Centers
- Autoimmunity Centers of Excellence
- Stem Cell Transplantation for Autoimmune Diseases Consortium

Basic and Clinical Immunology

- Cooperative Centers for Translational Research on Human Immunology and Biodefense
- Hyperaccelerated Award/Mechanisms in Immunomodulation Trials
- Vaccine Immunology Basic Research Centers

Immune Tolerance

- Immune Tolerance Network
- Innovative Grants on Immune Tolerance
- Nonhuman Primate Immune Tolerance Cooperative Study Group

Primary Immunodeficiency Diseases

- Primary Immunodeficiency Diseases Consortium
- PID Registry—USIDNET

Transplantation

- Cooperative Clinical Trial in Pediatric Kidney Transplantation
- Clinical Trials in Organ Transplantation
- Genomics of Transplantation Cooperative Research Program

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

Mission

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV. DMID supports a wide variety of projects spanning the spectrum from basic research through applied research, along with the development and clinical evaluation of new drugs, vaccines, and diagnostics. NIAID also funds projects to sequence the full genomes of a number of medically important microbes, which can be exploited in many ways—for example, to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiologic and biochemical processes. Studies on these pathogens extend basic insights to identify vaccine candidate antigens and drug targets and to examine mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include streptococci, pneumonia, nosocomial (hospital-acquired) infections, fungal infections, antibiotic resistance, bacterial sexually transmitted infections, and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and reproduction of viruses; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic information is being used to combat important viral diseases such as influenza, herpes, congenital cytomegalovirus infection, hepatitis, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens and to the development of more effective drugs. In addition, studies of arthropod vectors are aimed at controlling the transmission of important pathogens such as the malaria parasite.

One of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents: bacteria, viruses, fungi, and parasites. Since 1981, DMID has supported a program for the accelerated development of new vaccines to direct advances in molecular biology, immunology, genetics, and epidemiology. An integral component of these efforts is vaccine safety, which is evaluated in every vaccine clinical trial sponsored by NIAID.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for STIs and Lyme disease and the development of antimicrobial resistance markers.

Finally, DMID maintains a drug development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies in humans).

Scientific Areas of Focus

Biodefense

As concern grows about the use of biological agents in acts of terrorism and war, Federal agencies are evaluating and accelerating measures to protect the public from the health consequences of such an attack. Our ability to detect and prevent infections that emerge as a result of bioterrorist incidents depends to a large degree on the state of biomedical science. Basic

and applied research supported by the NIH complements the efforts of other Federal agencies by developing the essential tools—diagnostics, therapeutics, and vaccines—that are needed by physicians, nurses, epidemiologists, and other public health workers to prevent and control outbreaks of disease. NIAID is the primary NIH Institute that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by a wide variety of emerging pathogens, including those that could be intentionally introduced.

In response to the need for rapid development of resources for biodefense, NIAID continues to expand its research related to potential agents of bioterrorism as part of a broad research agenda involving other agencies within the Department of Health and Human Services and the Department of Defense. The components of the NIH's biodefense research program include development of biodefense-relevant diagnostics, therapeutics, and vaccines, as well as genomics, basic research on potential agents of bioterrorism, and infrastructure to support advanced research. Recent NIAID programmatic accomplishments include support for bioinformatics and proteomic resource centers; expansion of the Vaccine and Treatment Evaluation Units to accommodate testing of vaccines such as those for smallpox and anthrax; development of several new animal models for diseases caused by Category A, B, and C agents; support for grants and public-private partnerships for early product development through clinical trials of biodefense vaccines and drugs; a centralized repository to acquire, authenticate, store, and distribute NIAID Category A, B, and C agents to the scientific community for use in research and product development; and the expansion of research capacity through the multimillion dollar Research Centers of Excellence (RCEs) and National and Regional Biocontainment Laboratories (NBLs and RBLs) across the United States, which will provide critical resources for biodefense and emerging infectious disease research.

Emerging and Re-emerging Infectious Diseases

Emerging infectious diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Recent outbreaks of severe acute respiratory syndrome (SARS) and avian influenza in Asia and monkeypox in the United States are examples of emerging infectious diseases, while tuberculosis and pertussis are examples of diseases that have re-emerged after a period of decline. Factors involved in the emergence and re-emergence of infectious diseases include evolution of microbes; changes in vaccine compliance; overuse of antimicrobials; and changes in the interactions between humans and the environment due to human population growth, density, and contact with animal vectors or animals that may serve as disease reservoirs.

Both emerging and re-emerging diseases have significant implications for domestic and global health. DMID supports a broad spectrum of basic research on infectious diseases, including studies of epidemiology; pathogenesis; transmission and microbiology of emerging infectious diseases; and applied and clinical studies to develop and test vaccines, diagnostics and therapeutics for these diseases. Examples of DMID-supported research on emerging infectious diseases include robust research programs in SARS, West Nile virus, Lyme disease, and influenza. In 2003, DMID also provided funding for multiple RCEs, NBLs and RBLs across the United States, where scientists will be able to safely conduct critical research on emerging infectious diseases and NIAID Category A–C Priority Agents.

Vaccine Research and Development

DMID supports an active program of basic and applied research for the accelerated development of new vaccines, taking advantage of advances

in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program contributes to the development of new vaccines for a wide variety of bacterial, viral, and parasitic diseases, including SARS, malaria, West Nile virus, herpes, and pneumococcal pneumonia. DMID also supports research to develop novel vaccine delivery methods, such as transcutaneous skin patches and nasal vaccines. One example of NIAID's success in developing innovative vaccines is the recent licensure by the Food and Drug Administration of the FluMist intranasal influenza vaccine, for which much of the research and early development was supported by NIAID. DMID also supports a large national and international network for clinical trials of safety and efficacy of vaccines. Recent expansions of the network will allow more trials focused on specific populations and larger clinical trials, including those for biodefense vaccines. DMID's *Jordan Report*, now in its 20th anniversary edition, is a unique resource developed by the Division to inform the public health community and the general public of recent developments and the state of the science in vaccine research. This report can be viewed online at *www.niaid.nih.gov/dmid/vaccines/jordan20*.

Antimicrobial Drug Resistance

Emergence of drug-resistant infectious agents is becoming an increasingly important public health concern. Rapid evolution of microbes and misuse of antibiotics are major contributors to the rising number of resistant pathogen strains. Tuberculosis (TB), gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat because of the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired infections. Also, drug resistance that was almost exclusively hospital- or healthcare-associated is appearing and originating with increasing frequency in the community, such as community acquired methicillin resistant *Staphylococcus aureus*. Many physicians are concerned that several bacterial infections soon may be untreatable with currently available drugs.

NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens, including antimicrobial resistance among the major healthcare-associated bacterial pathogens. Specifically, NIAID supports investigator-initiated research on the molecular mechanisms responsible for drug resistance, as well as research to develop and evaluate new or improved therapeutics for disease intervention and prevention. Studies on several key organisms of interest seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistant genes. In August 2004, NIAID held the second Summit on the State of Anti-Infective Development to address the important issue of antimicrobial availability and to help determine the best ways for NIAID to address the key needs. NIAID also continues to participate in an interagency task force for the development of public health strategies for antimicrobial resistance. *The Public Health Action Plan to Combat Antimicrobial Resistance,* developed by the task force, describes issues, goals, and action items in surveillance, prevention and control, research, and product development, as well as a plan for interagency and industry coordination in addressing this critical health issue. The action plan is available online at *www.cdc.gov/drugresistance/actionplan/index.htm*.

Global Health

NIAID has developed a comprehensive global health research plan to address key issues in international health. Many of these activities focus on vaccine development. Genomics, microbial physiology, epidemiology and natural history, transmission/vector control, and development of improved diagnostics and therapies also are important areas of emphasis. Diseases of international health importance present additional scientific and logistical

challenges, such as access to endemic sites and populations. The Institute supports field-based research through investigator-initiated grants, disease-specific initiatives, and special programs, such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers.

DMID supports a broad portfolio of research in both TB and malaria. Areas of emphasis in DMID's TB research include basic biology of the TB pathogen and drug-resistant strains, disease progression, diagnostics, vaccines, therapeutics, epidemiology, and genomics. The NIAID Tuberculosis Research Unit supports an international, multidisciplinary team of collaborators to translate basic research findings into clinical studies. Current research activities sponsored by NIAID for malaria include drug development, pathogenesis research, vaccine development, epidemiology, and vector control. NIAID also supports the International Collaborations in Infectious Diseases Research program and the Tropical Medicine Research Center program to develop and evaluate new diagnostics, prevention, control, and therapeutic methods for tropical infectious diseases. These programs also provide training to international scientists and build capacity for independent research at overseas field sites.

Sexually Transmitted Infections

Sexually Transmitted Infections (STIs) are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with AIDS. Scientists now believe that people who have STIs are at an increased risk of contracting HIV/AIDS. DMID's STI research emphasis is on vaccine development and on clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STIs and conditions associated with having STIs, including pelvic inflammatory disease, infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infection, and the spread of HIV. A public-private partnership between NIAID and GlaxoSmithKline currently is supporting a phase III clinical trial for a new genital herpes vaccine for women. This has the potential to prevent a disease that is estimated to affect 45 million people in the United States aged 12 years and older and has significant health implications for infants. NIAID also supports a topical microbicide research effort to prevent STIs; this effort encompasses basic product development and clinical research.

Pathogen Genomics

In 1995, the first microbe-sequencing project, *Haemophilus influenzae* (a bacterium causing upper respiratory infection), was completed with a speed that stunned scientists. Encouraged by the success of this initial effort, researchers have continued to sequence an astonishing array of other medically important microbes. NIAID has made a significant investment in large-scale sequencing projects and includes projects to sequence the full genomes of many pathogens, including the bacteria that cause TB, gonorrhea, chlamydia, cholera, agents of bioterrorism, and viruses that cause flu. In addition, NIAID collaborates with other funding agencies to sequence larger genomes of pathogenic fungi, protozoan pathogens such as the organism causing malaria, and invertebrate vectors of infectious diseases.

The availability of microbial and human DNA sequencing in publicly-accessible databases has opened up new opportunities and allows scientists to examine functional analysis of genes and proteins in whole genomes and cells, as well as the host immune response and an individual's genetic susceptibility to pathogens. When scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins or to use those proteins as candidates for vaccines. Comparative genomic analysis of

microbes also can be used to study the spread of a virulent or drug-resistant form of a pathogen.

NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics and proteomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools and databases to allow investigators to have easy access to sequence and functional data for analysis. In summary, DMID supports a breadth of research activities on a variety of pathogens of importance in basic microbiology and infectious diseases.

DIVISION OF INTRAMURAL RESEARCH

Mission

Scientists in NIAID's Division of Intramural Research (DIR) *(www.niaid.nih.gov/dir)* conduct laboratory and clinical research covering a wide range of biomedical disciplines related to infectious diseases, immunology, and allergy. For example, DIR scientists conduct basic laboratory investigations to understand the biology and genetics of the viruses, bacteria, parasites, and fungi that cause infectious diseases. They also study the ticks, mosquitoes, fleas, and flies that transmit diseases such as West Nile fever, plague, and malaria. In addition, DIR has a large program focused on investigations of prion diseases, such as "mad cow" disease and chronic wasting disease of deer and elk, which are caused by a transmissible agent that has little in common with conventional infectious microbes.

Much of the research in DIR involves investigation of the multitude of interacting cells, antibodies, proteins, and chemicals that compose the immune system. A fundamental understanding of this intricate system is key to the development of therapies and vaccines for infectious diseases and critical to deciphering and treating immune system disorders—from mild allergies to life-threatening immunodeficiencies. The ultimate goal of the Division's research is to contribute to the development of new and improved therapies, diagnostics, and vaccines that will improve health, save lives, and enhance the quality of life in the United States and worldwide. This contribution may take the form of delineating a cell signaling pathway, discovering the function of a tick gene, determining the three-dimensional structure of an immune cell receptor, or finding the enzyme malfunction causing a primary immunodeficiency.

Translating laboratory research findings to the clinical arena is accomplished through the facilities of the Warren Grant Magnuson Clinical Center on the NIH campus. There, physician-scientists treat patients with a variety of diseases, including AIDS, host defense defects, asthma, various parasitic diseases, and disorders of inflammation. NIAID currently has more than 80 active clinical protocols, under which patients participate in studies of new and promising treatments or diagnostic procedures, often derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the superb scientific setting at the NIH while they participate in DIR's basic and clinical research programs.

The Division and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

Scientific Resources

Each of the 17 DIR laboratories (*www.niaid nih.gov/dir/labs.htm*) has project-specific resources that are augmented by the expertise and services provided to all DIR labs by supporting branches. The DIR branches offer access to state-of-the-art technologies for peptide synthesis, protein sequencing, mass spectroscopy analysis of peptides and small molecules, electron microscopy, confocal microscopy, flow cytometry and cell sorting, and DNA microarray. The branches also provide genetically modified (transgenic as well as knockout/knockin) mice, extensive in-house animal breeding and holding facilities (including nonhuman primate), oversight of animal protocols, and support to

scientists conducting animal studies. Animal care facilities, including biosafety level 3 facilities, are maintained in Bethesda, Maryland, and at DIR laboratories in Hamilton, Montana. In addition to the facilities directly managed by NIAID, DIR investigators have access to NIH-wide facilities such as the Mouse Imaging Facility. Investigators wishing to interact directly with other scientists in a very focused setting can do so by joining one of the more than 80 NIH scientific interest groups organized around specialty areas.

Computer linkages for DIR scientists consist of a local area network within NIAID and a wide area network linking DIR scientists to other areas of NIH, such as the computer facilities of the NIH Division of Computer Research and Technology. The computer network also provides quick access to the libraries of the NIH Clinical Center and to the National Library of Medicine and links DIR researchers in the Maryland locations of Bethesda, Rockville, and the Frederick Cancer Research and Development Center and in the Rocky Mountain Laboratories in Hamilton, Montana. Teleconferencing equipment further enhances communications between DIR staff members and their colleagues across the campus and around the world. In addition, DIR investigators communicate with colleagues at the Malaria Research and Training Center in Mali via direct satellite uplinks, which are much faster and more dependable than the local Internet service provider connections.

Scientific Areas of Focus

Immunology Research

Immunology research is inextricably linked to studies of infectious diseases and allergy. In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, the findings enhance the understanding and development of effective treatments for immunodeficiency diseases in which the immune cells are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Current investigations include the following:

- Functional studies of regulatory T cells;
- Innate immune response to pathogenic bacteria;
- Animal models of autoimmune diseases; and
- Novel therapies for primary immunodeficiencies.

Allergy Research

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on the mast cell, which plays an important role in many allergic disorders and secretes chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in the connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. Studies include the following:

- Cytokine profiles of allergic diseases;
- Tolerance studies for asthma;
- Development of mast cell lines for use in drug discovery; and
- Pathogenesis of food allergy.

Infectious Disease Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing our understanding of pathogenic organisms, host response to infection, vector biology, and chemotherapeutics. Studies of the microorganisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, West Nile fever, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the organism that are necessary for reproduction. Host studies may define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies may reveal new targets for public health interventions. Application of this multidisciplinary approach to investigations of new and re-emerging infectious diseases and biodefense studies is a top DIR priority. DIR scientists are collaborating with colleagues from government, academia, and industry to develop vaccines, diagnostics, and therapeutics for high-priority pathogens and to conduct the basic laboratory research that provides the foundation for product development. In addition, DIR scientists are engaged in collaborative research in a number of developing countries with a high infectious disease burden. Additional information about DIR studies of biodefense research and emerging infectious diseases can be found on pages 54 and 71, respectively. Other ongoing projects in DIR include the following:

- Structured therapy interruption as an AIDS treatment strategy;
- Development of more effective drugs for tuberculosis;
- Pathogenesis and cross-species transmissibility of prion diseases or transmissible spongiform encephalopathies; and
- Genetics of drug resistance, antigenic variation, and disease severity in malaria.

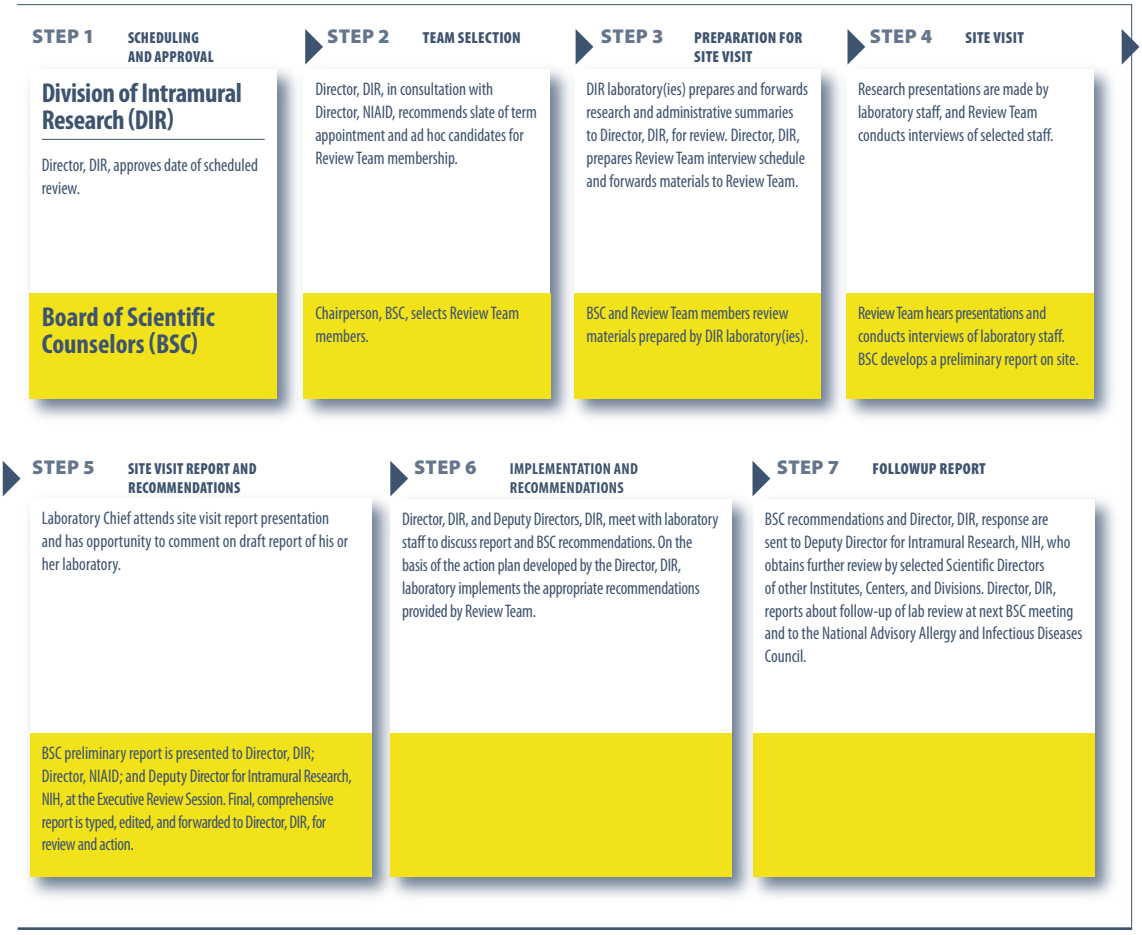
Vaccine Research

Candidate vaccines against many infectious agents of public health importance are undergoing laboratory and clinical testing in DIR. These include vaccines for respiratory and gastrointestinal viruses, hepatitis viruses, and infectious agents that cause common tropical diseases such as malaria and dengue. DIR scientists also are collaborating in the development of vaccines to prevent the natural or deliberate spread of infectious diseases such as smallpox, severe acute respiratory syndrome (SARS), plague, and pandemic influenza. Studies are under way to develop vaccines against pathogenic flaviviruses such as the West Nile virus, St. Louis encephalitis virus, and tick-borne encephalitis virus. Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in DIR. For additional DIR information, see page 133.

Laboratory Review Process

The following chart provides information on DIR's laboratory review process:

DIVISION OF INTRAMURAL RESEARCH LABORATORY REVIEW PROCESS



DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

Mission

The Dale and Betty Bumpers Vaccine Research Center (VRC) (*www.vrc.nih.gov*) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. There are an estimated 5 million new HIV infections each year, and in 2004 the disease resulted in an estimated 3 million deaths.[1] Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond patients' financial reach. Therefore, effective, low-cost tools for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge forms the basis for new ideas that could lead to novel strategies for effective vaccination. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective vaccine. In this setting, VRC has a unique opportunity and responsibility to facilitate the transition of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

HIV strains worldwide display tremendous genetic diversity that may limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished: these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, while HIV-1 is the cause of the global pandemic. HIV-1 is classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce effective immunity in a large percentage of the population. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

Development of an effective vaccine against HIV is the primary mission of VRC. To this end, VRC collaborates closely with the NIAID Division of AIDS (DAIDS), particularly with regard to regulatory support and implementation of clinical trials through established trial networks. In addition to its research program for HIV/AIDS, VRC's research programs in biodefense have been expanded, intensified, and accelerated. For example, VRC, working closely with the NIAID Division of Microbiology and Infectious Diseases (DMID) and with industry partners, is positioned to make substantive contributions in the development of vaccines protecting against Category A and B agents such as smallpox, West Nile virus, and hemorrhagic fever viruses (such as Ebola) posing a potential bioterrorist threat.

VRC also is collaborating closely with DMID and the NIAID Division of Intramural Research to develop a vaccine for severe acute respiratory syndrome (SARS).

Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this development process has been successful to combat numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology that takes advantage of the latest technologies and scientific knowledge to design effective vaccine strategies is now emerging. This process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance. By having diverse components of vaccine research, development, production, and evaluation readily accessible at one site, along with a group of committed investigators with diverse skills but a common goal, VRC has embarked on a comprehensive and systematic approach to vaccine development.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, is being established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with clinical trials methodology. By encompassing these activities at a single center possessing the capacity for vaccine production, VRC hopes to advance the science of vaccine development.

The same infrastructure being employed to develop an effective HIV vaccine also is being deployed in the search for an improved smallpox vaccine and for effective vaccines against Ebola, West Nile virus, and SARS.

Research Goals and Objectives

VRC has four broadly encompassing research goals, each of which has multiple subparts. The goals are as follows:

- Goal 1: Scientifically design and develop effective vaccine candidates.
  - Use knowledge of the HIV envelope structure to design immunogens that elicit potent virus-neutralizing antibodies through a program of rational structure-based design and screening of immunogens.
  - Develop and optimize gene-based vaccine platforms that elicit broad and potent cell-mediated and humoral immunity.
  - Use state-of-the-art methods in genomics and bioinformatics to advance vaccine development.
- Goal 2: Evaluate and optimize the immune response generated by candidate vaccines.
  - Identify and develop validated, reproducible methods to quantitate vaccine-induced immune responses in humans and primates.
  - Identify vaccine candidates and immunization strategies that enhance

potency, antigen presentation, and immunogenicity.

  - Develop rational use of the primate model to assess vaccine strategies and define immune correlates.

- Goal 3: Advance the most promising vaccine candidates into human clinical trials.

  - Develop the infrastructure to produce and test vaccine products.

  - Conduct clinical evaluation of candidate vaccines.

  - Evaluate preventive vaccine candidates in clinical protocols of therapeutic immunization.

- Goal 4: Create the necessary infrastructure for translating basic research to the clinical setting.

  - Establish a contractor-leased and operated Vaccine Pilot Plant (VPP) as a high priority for VRC. VPP will manage production of multiple vaccine candidates originating from VRC. To achieve this objective, VPP will provide research and development services to the Vaccine Production Laboratory located on the Bethesda campus to assist in transferring new vaccine technology for pilot-scale production of clinical trial material. VPP is being designed as a leased pilot plant in Frederick, Maryland, with an anticipated completion date of late 2005. At completion, the VPP will be a self-contained facility of 126,900 square feet with the capacity to produce 4 to 8 clinical lots of vaccine annually. Vaccines produced at the VPP will support phase I and II clinical trials. In addition, the facility will incorporate design features that will allow conversion to larger scale operations capable of supporting phase III trials, if necessary.

Basic Research

Acquired Immunodeficiency Syndrome

VRC aims to develop vaccine candidates that will induce effective humoral responses (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program explores basic science questions relevant to vaccine design. Guided by continuing research that reveals a better understanding of the basic elements of protective immunity, scientists at VRC apply this knowledge toward the design of vaccines.

The VRC program in virus structural biology explores the rational design of vaccines that can induce potent virus-neutralizing antibodies. Using innovative crystallographic techniques, the structure of gp120, an important viral protein on HIV's surface, has been determined at the atomic level, leading to the identification and visualization of numerous overlapping mechanisms of immune evasion. VRC is using this and other structure-based analyses and protein-based principles to assist in the rational development of novel candidate vaccines for HIV. This approach also is being applied to the development of vaccines against other pathogenic viruses of public concern.

Development of candidate vaccines focuses on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered using immunization

with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines. Such preclinical animal testing is closely integrated with VRC's basic science programs to provide information for iterative improvements in the development of new candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV is guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. The development of reproducible, validated assays to measure T cell function and virus particle reduction is key to successful evaluation of both animal studies and human clinical trials. The VRC Immunology Core is currently designing, optimizing, and performing immunologic assays that measure the two major types of immune responses—cellular and humoral. Candidate vaccines are being evaluated by intracellular cytokine staining, ELISPOT assays, and measurements of neutralizing and binding antibodies. VRC also is expanding current assays to be applicable to more antigens and various clades of HIV as well as exploring ways to optimize and automate assay performance using state-of-the-art technologies in robotics.

Using these newly developing technologies, scientists can determine how effectively a candidate vaccine protects against infection or disease.

Ongoing preclinical studies in small animals and primates are evaluating vaccine dose, formulation, and delivery route and addressing the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies will be used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing will be integrated closely with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

The gene product Murr1 restricts HIV-1 replication in resting CD4+ lymphocytes. The human immunodeficiency-1 (HIV-1) virus replicates poorly in resting T cells. Factors that block viral replication in these cells might help to prolong the asymptomatic phase of HIV infection. NIAID scientists have identified and characterized a protein, Murr1, which is involved in the regulation of NFκB and HIV-1 infection. Murr1 acts as a genetic restriction factor that inhibits HIV-1 replication in lymphocytes, which could contribute to the regulation of asymptomatic HIV infection and the progression of AIDS. Research is ongoing to understand the role of Murr1 in HIV-1 infection and to define pathways of molecular regulation of HIV-1. This will help identify targets through which anti-viral drugs may delay the progression of HIV-1 infection to AIDS. Such an understanding will be useful in the development of drugs that can help in the treatment of AIDS, as well as of other viruses, such as Ebola, dengue, and cytomegalovirus.

Scientists identify strategies for human antibodies to overcome HIV-1 defense mechanisms. HIV-1 utilizes a variety of defense mechanisms to evade the immune system, which poses a significant challenge to the development of an effective vaccine. The immune system produces antibodies against foreign molecules such as HIV. The primary target of antibody recognition is gp120, a protein on the envelope

surface of the virus. Using various structural analyses, scientists have identified two novel mechanisms that allow antibodies to overcome HIV-1's defenses and enhance recognition of the virus. Selection and usage of a gene called V_H and addition of a sulfate molecule to part of the gp120 protein have been demonstrated to enhance antibody recognition, therefore providing new targets for HIV-1 vaccines and therapeutics.

Ebola and Other Viral Hemorrhagic Fevers

Outbreaks of Ebola in Africa kill up to 90 percent of those infected. No effective treatment exists for this highly infectious disease, which causes extensive internal bleeding and rapid death. According to experts, vaccination is the best strategy for preventing or containing this deadly infection. Investigators at VRC, with scientific collaborators at the U.S. Army Medical Research Institute of Infectious Diseases, have developed a potentially effective vaccine strategy for Ebola virus infection in nonhuman primates. Previous VRC studies have shown that a combination of DNA vaccination and boosting with adenoviral (ADV) vectors that encode viral proteins was protective against Ebola viral challenge and generated cellular and humoral immunity in cynomolgus macaques.

West Nile Virus

The NIAID Vaccine Research Center is currently conducting preclinical testing of a West Nile virus vaccine. The VRC proposes to use an existing codon-modified gene-based DNA plasmid vaccine platform to make DNA constructs that express West Nile virus proteins. These vaccine constructs are currently undergoing immunogenicity and viral challenge studies in rabbits. The VRC in collaboration with Vical, Inc. has completed GMP production of the vaccine for a phase I trial scheduled for early 2005.

SARS

In response to the recent global outbreak of SARS (Severe Acute Respiratory Syndrome), VRC Investigators quickly began working on the development of a potential vaccine. A Cooperative Research and Development Agreement and contract have been established with GenVec, Inc. GenVec is producing preclinical and clinical grade adenoviral vectors that express several SARS proteins. The VRC 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 is being planned for late 2004 or early 2005.

Clinical and Regulatory Infrastructure

VRC has assembled a full clinical research support team consisting of physicians, study coordinators, nurse practitioners, research nurses, and recruitment and outreach specialists. These staff represent VRC at community events, screen potential volunteers, and perform vaccinations and subsequent follow-up and testing of enrolled volunteers. VRC also has developed the strong regulatory infrastructure required to support the development and testing of vaccines. In collaboration with DAIDS and DMID, VRC staff members manage the submission of Investigational New Drug (IND) applications to the Food and Drug Administration (FDA), develop protocols for human clinical trials, and ensure that all studies are performed in accordance with FDA guidelines, while meeting all applicable reporting requirements.

Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, VRC combines traditional empirical vaccine development with hypothesis-driven basic and preclinical research. This approach promotes an iterative process in which data from clinical evaluation will inform basic research and vaccine design, and findings in animal models will help prioritize approaches to test in clinical trials. In addition to traditional phase I studies in HIV seronegative volunteers, VRC has been studying the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4 and CD8 immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T cell memory that play a role in protection against HIV. Such data then can be applied to the development of therapeutic and preventive vaccines.

VRC actively collaborates with both intramural and extramural scientists and facilitates the movement of ideas from the broader community into clinical trials. Close ties are maintained with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale trials already is established. This collaboration will include efforts to develop vaccine candidates that can be evaluated at international field sites. When products emerge with real promise for licensure, VRC also will interact with the pharmaceutical industry, in which there is a large capacity for and experience in product development and distribution. Therefore, VRC is working to fill the gap between new basic concepts in immunology and initiation of clinical trials by applying state-of-the-art methods to rational vaccine design and evaluation at a single site.

Acquired Immunodeficiency Syndrome

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 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 at the National Institutes of Health in Bethesda, MD, and is designed to determine the vaccine's safety at 3 dose levels. All 50 healthy, HIV-negative volunteers have completed clinical follow up and the study has recently been unblinded. A larger clinical trial to further evaluate safety, immune response, and schedule is being conducted through the DAIDS, 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.

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.

Ebola

In November 2003, the VRC initiated the first human trial of a vaccine designed to prevent Ebola infection. The trial is currently fully enrolled and to date, the injections have been well tolerated. In addition to testing preventive vaccine candidates, the VRC is currently developing a vaccine that might be useful in an acute outbreak setting. For example, a recently tested candidate (a single vector ADV-only) vaccine elicited protective immunity in monkeys after a 4-week postvaccination challenge, in contrast to previous 10-week or 6-month vaccine regimens. A second-generation product that would provide coverage for Marburg and possibly Lassa virus may also be evaluated.

MVA

VRC currently is testing modified vaccinia Ankara (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 VRC and DMID. Two phase I clinical trials are now underway testing MVA as a component of a safer smallpox vaccine in both vaccinia-naive and vaccinia-immune populations. Scientific collaborations have been developed with both DMID and private-sector partners for the development and production of MVA as a component of a safer smallpox vaccine for further clinical testing. Following the completion of the current phase I trials, further development of MVA as a component of a safer smallpox vaccine will be directed by DMID.

New Initiatives

VRC is planning new initiatives to support the growing needs of its expanding mission. VRC currently conducts phase I vaccine studies on the NIH Bethesda campus. In preparation for the conduct of phase II and III studies and to manage the complex activities related to international vaccine development, VRC has created a team dedicated to advanced clinical development of candidate vaccines.

To further support research and development on vaccines for smallpox, Ebola, and West Nile virus, an additional laboratory dedicated to biodefense research is currently being formed, with the purpose of accelerating both basic research and subsequent development of biodefense-related vaccines.

Human Clinical Trials and Licensure of an AIDS Vaccine

VRC is working closely with its scientific collaborators and with FDA to discuss the potential for expedited approval of AIDS vaccines. The carefully considered use of surrogate end points (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate end points can accrue from well-designed trials, and this information can be applied to the design of future trials.

[1] UNAIDS. AIDS epidemic update: 2004. Available at *http://unaids.org/wad2004/report.html*

DIVISION OF EXTRAMURAL ACTIVITIES

Mission

The Division of Extramural Activities (DEA) (*www.niaid.nih.gov/ncn*) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's research training and international programs, and conducting initial peer review for funding mechanisms with Institute-specific needs.

In addition to providing broad policy guidance to Institute management, DEA also oversees NIAID's chartered committees, including the National Advisory Allergy and Infectious Diseases Council (NAAIDC); disseminates information to its extramural community through its large Internet site; and conducts extramural staff training and communications through the NIAID intranet.

DEA staff members interact intensively with grantees, contractors, reviewers, NAAIDC members, applicants, and staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome; the Division of Allergy, Immunology, and Transplantation; and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch (GMB) issues all NIAID grant awards after negotiating the terms of the award with grantees. GMB specialists determine award amounts, develop administrative terms and conditions, and release official award documents. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowed and how to formulate a budget for an application. GMB specialists supervise the day-to-day administration and financial management of Institute grants and cooperative agreements, while ensuring that grants comply with existing policies.

The Contract Management Program (CMP) (*www.niaid.nih.gov/contract*) manages the administrative aspects of NIAID's research and development contract portfolio. CMP specialists help develop requests for proposals, negotiate technical and business aspects of proposals, and select proposals for funding. Contract specialists are well-versed in legal, technical, business, and cost-related topics, including Federal Acquisition Regulations. They provide investigators with guidance on changes in the scope of the research, the use of funds, and other administrative issues.

The Scientific Review Program (SRP) conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications (RFAs) and requests for proposals (RFPs). Scientific review administrators assist NIAID staff members with the design, development, and review of initiatives. They also conduct initiative phasing, perform quality control of RFAs and RFPs, and formulate peer review strategies.

The Referral and Program Analysis Branch (RPAB) handles receipt and referral for grant applications that undergo initial review at NIAID. RPAB also performs scientific classification and data analysis of NIAID's funded grants, contracts, and intramural research projects for official science-information reports.

Several offices and staff members in DEA's Office of the Director (OD) play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including innovative electronic systems. In addition, the OD is a long-time leader in developing

innovative technologies that have been adopted by the NIH, including electronic peer review and acquisition systems.

- The Office of Special Populations and Research Training (OSPRT) (*www.niaid.nih.gov/facts/mwhhp.htm*) manages and awards fellowships (F), institutional training (T), and research career (K) grants. OSPRT provides oversight and coordination for NIAID's minority and women's health activities and initiatives and manages research supplements for underrepresented minorities and scientists with disabilities.

- The Office for Innovation and Special Programs manages grants for NIAID's small business programs—Small Business Innovation Research and Small Business Technology Transfer.

- The Office of International Extramural Activities (*www.niaid.nih.gov/ncn/grants/int/default.htm*) helps develop policies for international applicants and grantees. It reviews the financial systems of non-U.S. grantees and communicates with other Federal agencies about international polices for select agents.

- The Office of Knowledge Resources (OKR) informs the Institute and its extramural research community of funding opportunities, advice, policy updates, and other news. OKR provides budget and payline information as well as tutorials on NIH operations, planning and writing grant applications, and managing grant awards. The *NIAID Funding* newsletter and NIAID Funding Web site (*www.niaid.nih.gov/ncn*) are designed for the extramural research community, while the *NIAID Insider* newsletter and the *Inside Extramural* intranet (*intra.niaid.nih.gov/organization/dea*) are tailored to Institute staff.

- The Committee Management Office oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, and special emphasis panels. It also administers Scientific Review and Evaluation Awards.

- The Office of Data Quality and Initiative Development initiates, plans, designs, and oversees extramural research initiatives. It also performs review and quality control of solicited grant and contract initiatives.

- The Office of Scientific Resource Development (OSRD) develops Web-based and classroom training for NIAID staff and expands Institute learning resources. It educates NIAID staff on key scientific, clinical, and management mechanisms to enhance job performance.

- The Office of Program Coordination and Operations manages NIAID initiative phasing plans, develops NIAID Council guidance and timetables, manages the grants records center, and works with the administrative office to manage daily functional activities.