DRUG RESEARCH AND DEVELOPMENT

The discovery of sulfanilamide, penicillin, and other antibiotic drugs in the early 20th century revolutionized the treatment of infectious diseases and gave doctors powerful new tools that for the first time allowed them to easily defeat bacterial infections that would otherwise have been life-threatening. More recently, drugs have been developed that can combat viruses such as influenza and HIV, as well as fungal and parasitic infections. Unfortunately, many infectious agents have become resistant to current therapies, thereby threatening to destroy the effectiveness of these original "wonder drugs." Also, the immune system can itself cause illnesses such as diabetes, arthritis, and multiple sclerosis when it inappropriately attacks the body's own tissues.

The development of new therapies for the treatment of infectious and immune-mediated diseases is therefore one of NIAID's highest priorities. Basic research is the foundation for drug development. Through scientific advances in microbiology, virology, and immunology, scientists identify potential targets for therapeutic agents and new strategies for treating infectious and immune-mediated diseases. Often in collaboration with industry, academia, and other Government agencies, NIAID carries out many research programs that facilitate drug development, including databases of chemical structures that can be screened for use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trial networks to evaluate the safety and efficacy of drugs and therapeutic strategies. Because drug development is a key component of NIAID's mission, each NIAID division is actively involved in the drug development process.

Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes a substantial portion of its resources to the discovery and development of new therapies for people with HIV/AIDS, including AIDS-associated opportunistic infections, co-infections, and malignancies. DAIDS makes a special effort to provide funds to promising research strategies that receive insufficient support elsewhere.

A strong portfolio of basic research is the foundation for DAIDS' drug development activities. Over the past 15 years, drug discovery efforts have concentrated on a relatively small number of HIV targets, especially reverse transcriptase (RT), the enzyme that makes a DNA copy of the virus' RNA genome after it invades a cell, and protease (PR), the enzyme that activates immature HIV precursor proteins.

A combination of RT and PR inhibitors known as highly active antiretroviral therapy, or HAART, has revolutionized the treatment of people with HIV, successfully suppressing the virus and decreasing the incidence of opportunistic infections. These drugs, however, do not constitute a magic bullet. Many patients suffer metabolic abnormalities and toxicities, and some have difficulty adhering to the complex drug regimens required. Strains of HIV resistant to the therapy can also emerge.

Fortunately, new classes of therapeutic agents have recently entered the development pipeline. Some of these interfere with virus binding and entry into the cell, while others act on viral targets such as HIV integrase, an enzyme that incorporates the HIV genome into a host cell's DNA. Stopping HIV before it integrates into a host cell is an attractive strategy because it would potentially protect healthy cells from infection and thereby prevent immune system dysfunction. Therapeutic vaccines, which attempt to spur the immune system of an infected person to mount a more vigorous defense, are a potential immunologic approach to complement drug treatment. Even as these advances continue, so, too, does the need for new host and viral targets, novel drugs and delivery systems, and

immunologic approaches to address the dual problems of drug resistance and toxicity.

The pathways that lead to new HIV drug therapies are many and varied, but all begin with basic research. The studies include the structure and function of viral and cellular proteins critical to the HIV life cycle, immunopathogenic studies to understand how the virus disables the immune system, genetic studies—both human and viral—to define which genes affect susceptibility to infection and disease progression, and studies to understand how to restore effective immune function.

DAIDS pursues these approaches to targeted drug discovery through investigator-initiated grants, Small Business Innovation Research grants, and contracts. Current programs targeting therapeutics research on HIV/AIDS, its complications, and co-infections include the Novel HIV Therapies: Integrated Preclinical/ Clinical Program (IPCP); the Innovation Grants for AIDS Research program; the Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; the Liver and Pancreatic Disease in HIV Infection Program; the Complications of Antiretroviral Therapy Program; and the International Studies of AIDS-Associated Co-Infections Program (ISAAC).

The IPCP supports the preclinical evaluation, development, and pilot-stage clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair immune damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is identified and moves into preclinical development, it is systematically varied in small ways in an effort to improve its overall activity, safety, and effectiveness. These variations on a theme are subjected to additional *in vitro* testing, evaluating the agent's activity against a range of HIV isolates in different cell lines and animal models. If appropriate, the IPCP supports early clinical evaluation in human studies.

The Innovation Grants for AIDS Research Program supports research ideas that are new, innovative, or in the early stages of development, with the expectation that innovative research in these fields will increase understanding of the HIV pathogenesis and disease progression and provide new concepts for prevention and therapy. Targeted research for this program includes therapeutic discoveries, microbicide discovery, and HIV pathogenesis.

The Complications of Antiretroviral Therapy Program supports research in the fundamental biochemical or pathogenic mechanisms of the metabolic complications associated with HIV disease and antiretroviral therapy. Metabolic complications highlighted by this program include lipodystrophy (redistribution of body fat), insulin resistance, osteopenia (bone loss), abnormal lipid metabolism, and elevated lactate levels. This program is cosponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Drug Abuse, and the National Institute of Mental Health.

The ISAAC Program supports clinical studies of co-infections of HIV with one or more other pathogens such as tuberculosis (TB), other AIDS-defining opportunistic infections, malaria, and other parasitic infections endemic among adults and children in resource-constrained tropical countries. The long-term goals of ISAAC are to develop effective and sustainable clinical management strategies to improve local standards of care and to foster the integration of research for HIV and relevant co-pathogens. The program emphasizes training, technology development, and enhancing independent research capacities in host country sites.

The Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program stimulates preclinical research for novel therapeutic strategies against opportunistic infections, co-infections, and malignancies in people with HIV/AIDS.

This program is sponsored jointly with the National Cancer Institute and the National Institute of Dental and Craniofacial Research. The AIDS-associated infections this program emphasizes are *Mycobacterium tuberculosis (M. tb), Pneumocystis carinii, Cryptosporidium parvum*, and the microsporidia. The AIDS-associated malignancies program focuses on Kaposi's sarcoma, lymphomas, cervical cancer, oral warts and cancers, and anogenital cancers.

The Liver and Pancreatic Disease in HIV Infection Program is intended to stimulate research on the pathogenesis and therapeutics of liver and pancreatic disorders associated with co-infections that occur in HIV patients, as well as the metabolic complications associated with treatment of HIV infection. This program is sponsored jointly with NIDDK. The co-infections that this program emphasizes include hepatitis B and hepatitis C. Metabolic complications include hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis, and pancreatitis.

Contract resources are also devoted to supporting clinical research on therapeutic interventions for *M.tb* infection and co-infection with HIV (see, for example, *http://www.taacf.org*). This support includes high-throughput screening of anti-*M.tb* compounds and testing in animal models. For additional information on *M.tb* research, see the section on TB on page 121.

DAIDS also supports therapeutics discovery and development by helping to acquire and disseminate information on promising treatments for treating HIV infection and associated opportunistic pathogens. These activities include assisting drug sponsors in obtaining additional *in vitro* and *in vivo* activity data. DAIDS also keeps track of treatments in the pipeline by developing, maintaining, and using databases of chemicals with known or potential activity against HIV and associated opportunistic pathogens. DAIDS scientific staff members use these databases to monitor compounds already under investigation and to identify additional candidates. Information from the databases is available to the scientific community on request.

Once a therapy has been developed, DAIDS sponsors clinical trials to determine how well it improves the quality and duration of life for HIV-infected individuals; these clinical tests include studies to evaluate safety, dose, activity, efficacy, and optimal use. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Terry Beirn Community Programs for Clinical Research on AIDS. Together, these groups comprise the largest AIDS clinical trials network in the United States, if not the entire world.

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports the discovery and evaluation of new drugs for infectious diseases at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation. Because DMID's mandate encompasses a broad array of infectious diseases, the Division's drug development efforts address the entire spectrum of infectious diseases, including hepatitis, herpes, TB, sexually transmitted infections (STIs), malaria, fungal diseases, viral respiratory infections, hospital-associated bacterial infections, and pneumonia. Moreover, the Division's activities support all stages of drug discovery and development, from the test tube to the bedside and, especially for animal model and clinical research, involve close collaborations with the pharmaceutical industry and the Food and Drug Administration (FDA). Finally, in FY 2004, DMID supported approximately 40 large-scale genome-sequencing projects; the genomic information obtained has great potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

Discovery and Preclinical Evaluation

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against many different viruses, including herpes simplex viruses (HSV-1, HSV-2, varicella-zoster virus [VZV], Epstein-Barr virus, cytomegalovirus [CMV], human herpesvirus [HHV]-6, HHV-8); respiratory viruses (influenza A and B, respiratory syncytial virus, parainfluenza virus, measles, rhinovirus, adenovirus, sudden acute respiratory syndrome coronavirus); hepatitis B and C; papillomaviruses, BK virus, orthopoxviruses (vaccinia and cowpox); and other viruses that cause hemorrhagic fevers and encephalitides, including West Nile virus. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug discovery research and therapeutic evaluation efforts for HIV therapies.

DMID supports basic and applied research on the discovery and design of antiviral agents; these projects have led to the design of new drugs for influenza, CMV, poxvirus, and hepatitis. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. One part of a recent study, for example, included the development of a new mouse model for VZV infection in neurons. VZV causes both chickenpox and shingles; the new mouse model will increase our understanding of shingles and help in the development of new VZV vaccines and antivirals. Other recent findings have identified several drugs with activity against members of the poxvirus family, which might be helpful in the event of a bioterrorist attack using smallpox.

Basic research on pathogen replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites, which in turn opens up new possibilities for the development of drugs that attack these targets. For example, DMID-funded malaria researchers are working to identify the unique biochemical pathways in the malaria parasite that could serve as drug targets. They are also determining the mode of action of existing and potential drugs and mapping out the mechanisms by which the parasite has become resistant to existing drugs.

The emergence of antibiotic-resistant pathogens, including those that cause pneumonia and TB, has become a serious global health threat. Methicillin-resistant *Staphylococcus aureus*, for example, has rapidly emerged as a community-associated infection, and in two separate instances, *S. aureus* has acquired genes that make it resistant to the powerful antibiotic vancomycin. Public health officials fear that a strain of *S. aureus*—or some other pathogen—might arise that resists all antibiotics currently available.

In response, the Public Health Service, under the leadership of the NIH, FDA, and the Centers for Disease Control and Prevention, developed an antimicrobial resistance action plan that provides a blueprint for specific coordinated government actions to address the emerging threat. The four areas of emphasis are (1) surveillance, (2) prevention and control, (3) research, and (4) product development. NIAID has the lead in the area of research. The original plan, *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues,* as well as the second annual progress report and activity inventory are available online at *www.cdc.gov/drugresistance/actionplan*.

Prompt and accurate diagnosis of an infection is obviously important for good patient care, because it allows doctors to choose the right antibiotic. But good diagnostic tools also help to preserve the efficacy of drugs we currently have, by helping to limit the exposure of pathogens to inappropriate treatments, and can aid in the identification of patient populations for the evaluation of new antimicrobial agents. At the end of FY 2004, DMID began a new research initiative, called "Sepsis and CAP: Partnerships

for Diagnostics Development," that will support industry development of broad diagnostic technologies for early detection of major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia.

Clinical Studies

DMID supports clinical research with both individual grants and contract-supported programs such as the Collaborative Antiviral Study Group (CASG). The CASG, which evaluates antiviral drug therapies for neonatal and adult treatment of herpesvirus infections, is supported by a single award to the University of Alabama at Birmingham, and by subcontracts to more than 100 collaborating sites. The CASG also supports clinical trials that both assess the safety and efficacy of an experimental immunoglobulin treatment for West Nile virus encephalitis and help to elucidate its natural history.

The NIAID Mycoses Study Group (MSG), funded by both DMID and DAIDS, has supported clinical trials of antifungal therapies for opportunistic and endemic mycoses (fungal infections) since the 1970s. In early 2001, in conjunction with the scheduled completion of the MSG contract, two new contracts were awarded: the Bacteriology and Mycology Study Group (BAMSG) and the Bacteriology and Mycology Biostatistical and Operations Unit (BAMBU). BAMSG continues to conduct clinical trials of interventions for serious fungal diseases as well as healthcare-associated resistant bacterial infections. BAMBU provides biostatistical and administrative support for these clinical trials.

Other DMID-supported research groups that conduct drug and vaccine evaluations as part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, the Sexually Transmitted Diseases (STD) Cooperative Research Centers, and the STD Clinical Trials Unit. In 2000, NIAID launched a phase III efficacy trial using the STD Clinical Trials Unit to determine whether azithromycin, a drug approved for treatment of other infections, is as effective for syphilis therapy as the usual penicillin treatment; this trial continues to enroll patients. In FY 2003, NIAID launched a pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. This trial has expanded from 25 sites to 35 sites across the United States and is being conducted as a public-private partnership with GlaxoSmithKline, using DMID clinical sites. In addition, single-project grants and contracts support therapeutic evaluations for a number of other diseases.

Treatment-Related Research

The first step toward appropriate treatment of an infectious disease is the availability of a sensitive and specific diagnostic reagent. DMID supports many efforts to develop more effective diagnostic tools for infectious diseases. For example, DMID supports the development and manufacture of rapid, inexpensive diagnostic tests for STIs. The Division also supports research on topical microbicides, which are bactericidal or virucidal intravaginal preparations that would be used by women to prevent STIs.

In August 2004, NIAID hosted the Summit on the State of Anti-Infective Development in Bethesda, Maryland. The meeting was a followup to the Summit on Development of Infectious Disease Therapeutics, hosted by NIAID in 2000. The August summit brought together leaders from government and the pharmaceutical industry to assess the current state of antimicrobial development. A major focus of the meeting was the identification of both barriers to the development of new anti-infective agents, and opportunities for NIAID to work with the public and private sectors to help overcome those barriers.

Division of Allergy, Immunology, and Transplantation

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research and

development for drugs and biologics to treat and prevent diseases mediated by the immune system, such as autoimmune diseases, primary immunodeficiencies, asthma and allergic diseases, and rejection of transplanted organs, cells, and tissues. DAIT has established several collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of immunotherapeutic agents currently being evaluated in clinical trials.

Several investigations to evaluate new and potentially more effective therapies for asthma and allergic diseases are currently underway, including immune-based therapies and the development of new medications that inhibit or stimulate specific immune system biochemical systems. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to the prevention and treatment of autoimmune diseases. Researchers in these centers have expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes.

DAIT supports several clinical trials programs that test candidate therapies to limit immune-mediated morbidity and mortality of organ transplantation. These programs evaluate novel immunomodulatory strategies to prevent acute rejection and chronic graft loss. Strategies being examined include biological inhibitors of immune system activation, drug avoidance or minimization regimens to reduce problems associated with the immune system suppression needed to prevent rejection, and pre-transplant induction therapies to facilitate organ transplantation, prevent acute rejection, and promote immune tolerance. Through the Cooperative Clinical Trial in Pediatric Transplantation program, investigators are evaluating these strategies in children needing kidney transplants. DAIT and DAIDS cosponsor the Solid Organ Transplant in HIV program, which is implementing a multicenter prospective cohort study of kidney and liver transplantation in people with HIV. In FY 2004, DAIT, with cosponsorship from NIDDK and the National Heart, Lung, and Blood Institute, launched the Clinical Trials in Organ Transplantation program. This cooperative, multicenter consortium will design a research agenda to address transplantation generally as an immunologic disease rather than an organ-specific disease, and will conduct clinical trials and associated mechanistic studies in pediatric and adult organ transplant recipients. In FY 2004, DAIT and NIDDK launched the Clinical Islet Transplantation program, an international consortium that will design and implement human islet transplantation studies for improved treatment of type 1 diabetes mellitus. This consortium will accelerate research in immunosuppressive therapies to prevent rejection of the transplanted islets and the underlying autoimmune disease, and develop innovative approaches to islet isolation and preservation of islet graft function.

DAIT, in collaboration with NIDDK, supports the Nonhuman Primate Transplantation Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of new ways to induce immune tolerance of transplanted tissue, using preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2002, the program was expanded from 3 to 10 research grants, which has allowed more tolerance-induction strategies to be rigorously evaluated, improved sharing of valuable resources, and helped to forge new collaborations. To further accelerate the research conducted through this program, DAIT supports breeding colonies of specific pathogen-free rhesus and cynomolgus macaques.

DAIT, with cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International, continues to support the Immune Tolerance Network (ITN). ITN is an

international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection. The goal of tolerance-inducing therapies is to re-educate the immune system to eliminate harmful immune responses and graft rejection without reducing protective immunity to infectious agents. An important goal of ITN is to explore the immune mechanisms that cause candidate drugs to succeed or fail. ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia.

Division of Intramural Research

Much of the research underway in NIAID's Division of Intramural Research (DIR) is intended ultimately to aid in the development of more effective therapies for infectious and immunologic diseases. Much of DIR's effort is devoted to basic studies of the immune system; disease pathogenesis; and microorganism structure, replication, and transmission. These basic studies, however, often reveal potential new therapeutic targets for treating immunologic and infectious diseases. In addition, new technologies allow more precise characterization of the activity of current drugs, which may lead to the development of more effective formulations. For example:

- DIR scientists are studying the basic mechanisms underlying the effectiveness of current TB medications. They are also integrating new methods and information from genomics and combinatorial chemistry to speed development of second-generation therapeutics-based similar modes of action. New DNA microarray-based tools for deciphering the molecular mechanisms of anti-tubercular drugs will greatly facilitate these studies[23]. For additional information on TB, see the TB research section on page 121.

- Animal studies initially performed in DIR established that antibodies that bind to an immune system signaling molecule called IL-12 are an effective treatment of mucosal inflammation. Based on this finding, DIR, in collaboration with Wyeth Pharmaceuticals, participated in the development and clinical trial of a human form of the anti-IL-12 antibodies for treatment of patients with Crohn's disease. Phase I and II studies showed that the treatment is effective for active Crohn's disease, and pave the way for a phase III trial in a large patient cohort.[24]

- DIR clinicians continued to search for less toxic treatments for an autoimmune disease called Wegener's granulomatosis (WG). In an open-label study, patients were treated for active WG first using a standardized regimen of cyclophosphamide and prednisone to drive the disease into remission, followed by mycophenolate mofetil (MMF), an immunosuppressive agent currently used in the prevention of solid organ transplant rejection for remission maintenance. The use of MMF for remission-maintenance therapy may represent a less toxic alternative for patients with WG.[25]

- DIR scientists are developing agents to inhibit the cytokine IL-13 as a treatment for fibrosis in schistosomiasis, in which IL-13 is believed to be over-produced; other diseases in which this also occurs include asthma, idiopathic pulmonary fibrosis, and ulcerative colitis. Under a Cooperative Research and Development Agreement with Wyeth Research, the scientists plan to test several novel IL-13 inhibitors in the schistosomiasis model.[26]

In addition to these studies, DIR scientists are conducting more than 80 clinical research protocols at the Warren Grant Magnuson Clinical Center on the NIH campus. Many of these protocols are testing the efficacy of new drug therapies developed in DIR laboratories.