DRUG RESEARCH AND DEVELOPMENT

The development of therapies to treat infectious and immune-mediated diseases is a key component of NIAID's mission. Basic research serves as the foundation for drug development through scientific advances in microbiology, virology, and immunology. Advances in these areas help to identify potential targets for therapeutic agents and potential strategies for treating infectious and immune-mediated diseases. Through collaborations with industry, academia, and other Government agencies, NIAID has established research programs to facilitate drug development, including databases of chemical structures and chemicals that can be screened for potential 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.

Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes substantial resources to the discovery and development of new therapeutics for HIV/AIDS as well as AIDS-associated opportunistic infections, co-infections, and malignancies, attempting to focus resources on areas of promise that receive insufficient support elsewhere. A strong portfolio of basic research serves as the foundation for these activities.

Over the past 14 years, drug discovery efforts have concentrated on a relatively small number of viral targets: reverse transcriptase (RT), the enzyme that catalyzes the synthesis of viral DNA from the RNA template present in the incoming (or infecting) virion, and protease (PR), the enzyme that affects HIV maturation by cleaving and processing viral precursor proteins to their mature form. The combined use of RT and PR inhibitors (known as highly active antiretroviral therapy, or HAART) has been successful in suppressing HIV and decreasing the incidence of opportunistic infections. Nonetheless, complications have emerged with these antiviral agents, including the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of the required drug regimens. Moreover, damage to the immune system is only partially repaired by HAART. Recently, new classes of therapeutic agents have entered the development pipeline. These include agents that interfere with virus binding and entry into the cell as well as therapeutics directed at other viral targets such as HIV integrase, which is used by HIV to incorporate its genetic material into a host cell's DNA. Inhibition of HIV prior to integration is an attractive therapeutic strategy because it would potentially protect healthy cells from infection, thereby helping to bolster the immune system. In addition, therapeutic vaccines represent a potential new immunologic approach to complement drug treatment. Thus, while advances continue to be made, there remains an urgent need for the identification of new host and viral targets, novel drugs and delivery systems, and immunologic approaches to address the dual problems of drug resistance and toxicity.

HIV therapeutics are discovered through a number of approaches, beginning with basic research on the structure and function of viral and cellular proteins critical to the virus life cycle, immunopathogenic studies to further understand the nature of HIV-mediated immune deficiency, genetic studies to define

genes responsible for control of transmission susceptibility and disease progression, and strategies to restore or reconstitute effective immune function. These approaches are the foundation for targeted drug discovery, pursued 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 Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP); Innovation Grants for AIDS Research Program; Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; Liver and Pancreatic Disease in HIV Infection Program; Complications of Antiretroviral Therapy Program; and International Studies of AIDS-Associated Co-Infections Program.

The IPCP supports the preclinical evaluation, development, and pilot 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, the lead compound is subjected to an iterative process that improves the overall activity, safety, and effectiveness of the product. This is accomplished by additional *in vitro* testing, evaluating the agent's activity against a range of HIV isolates, testing the toxicity in different cell lines and animal models, and conducting pharmacologic studies. If appropriate, the IPCP supports early clinical evaluation in human studies.

The Innovation Grants for AIDS Research Program supports research ideas that are novel, innovative, or in the early stages of development, with the expectation that innovative research in these fields will affect understanding of the HIV pathogenesis and disease progression and provide new concepts for prevention and therapy. Targeted research for this program includes (1) therapeutic discoveries, (2) microbicide discovery, and (3) 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, insulin resistance, osteopenia, abnormal lipid metabolism, and elevated lactate levels. This program is co-sponsored by 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 International Studies of AIDS-Associated Co-Infections (ISAAC) Program will support clinical studies of the co-infections of HIV and one or more 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 the relevant co-pathogens. A major emphasis will be placed on training, technology development, and enhancing independent research capacities in host country sites.

The Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program is intended to stimulate iterative 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 emphasized by this program are *Mycobacterium tuberculosis (M.tb), Pneumocystis carinii, Cryptosporidium parvum,* and the microsporidia. The AIDS-associated malignancies emphasized by this program are 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 the liver and pancreatic disease associated with co-infections that occur in patients with HIV infection or the metabolic complications associated with treatment of HIV infection. This program is sponsored jointly with NIDDK. The co-infections emphasized by this program 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 *(www.taacf.org)*. These interventions include high-throughput screening of anti-*M.tb* compounds and testing in animal models. For more information on research on *M.tb,* please see the section on TB on page 133.

Another important element of the DAIDS therapeutics discovery and development effort is the acquisition and dissemination of information on agents or strategies that show potential 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 conducts a program of surveillance 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 entities to be pursued. Information from the databases is available to the scientific community on request.

Once a therapy has been developed, DAIDS conducts clinical trials to examine its effectiveness in improving the quality and duration of life for HIV-infected individuals. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). These programs investigate therapeutic agents and novel treatment approaches, including studies to evaluate safety, dose, activity, efficacy, and optimal use. Together, they represent the largest AIDS clinical trials network in the United States and probably in the world.

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports research to

facilitate the discovery and evaluation of new drugs for infectious diseases. This research is supported at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation. Current drug development efforts address a wide spectrum of infectious agents, including hepatitis, herpes, TB, sexually transmitted infections (STIs), malaria, fungal diseases, viral respiratory infections, and pneumonia.

The drug research and development efforts of DMID reflect the Division's broad purview and accordingly encompass a diverse range of target organisms and treatment strategies. The 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 colleagues from the pharmaceutical industry and the Food and Drug Administration (FDA).

DMID also supports approximately 36 large-scale genome-sequencing projects; this information has the 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 hepatitis B virus, hepatitis C virus, influenza, severe acute respiratory syndrome (SARS), respiratory syncytial virus, cytomegalovirus (CMV), vaccinia, 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.

DMID supports investigators conducting 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 infections. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. Two recent studies include the development of a guinea pig model that more closely mimics CMV infection in human newborns, which will be a valuable tool for understanding CMV infection as well as evaluating potential new drugs or vaccines; and the development of a unique chemical technology that generated a novel family of compounds (called oxazoline hydroxamic acids) as candidate inhibitors for LpxC, a vital enzyme for Gram-negative bacteria. 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 microbe replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites and of strategies to develop new agents based on this knowledge. For example, research projects on malaria include identification and characterization of unique parasite biochemical pathways that may serve as targets for drugs, determination of the mode of action of existing and potential drugs, and analyses of the mechanisms by which the parasite has become resistant to existing drugs.

An increasingly important contributor to the emergence of many infectious diseases,

including pneumonia and TB, is the emergence of drug-resistant pathogens. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. This situation is becoming an increasingly important public health concern. 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 plan that provides a blueprint for specific coordinated Government actions to address the emerging threat of antimicrobial resistance. 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 *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.*

Clinical Studies

DMID clinical research is supported either by individual grants or by contract-supported programs, such as the Collaborative Antiviral Study Group (CASG) and the Bacteriology and Mycology Study Group (BAMSG). The CASG is supported by a single award to the University of Alabama at Birmingham and by subcontracts to more than 100 collaborating sites. The CASG has recently established the safety and effectiveness of a new dose of the standard antiviral drug acyclovir, advancing the treatment of neonatal herpesvirus infections. In addition, the CASG has demonstrated that an anti-CMV drug can decrease hearing loss in infants with symptomatic congenital ear infection.

Currently, the CASG is evaluating new therapies for congenital CMV, herpes simplex encephalitis, respiratory syncytial virus, and hepatitis C virus infections. The CASG also recently began a clinical trial to assess the safety and efficacy of an experimental immunoglobulin treatment for West Nile virus encephalitis.

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

A phase I study evaluating a new monoclonal antibody treatment in patients who have recovered from AIDS-associated cryptococcal meningitis was conducted under the MSG and BAMSG contracts. New clinical trials in development include the following treatments: antifungal drugs and immune-based therapeutics, combination antifungal drugs for life-threatening fungal infections, and infection control strategies to reduce colonization and infection caused by multidrug-resistant bacteria in intensive care unit settings.

Other DMID-supported research groups that conduct drug evaluations as a 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, Azithromycin versus Benzathine Penicillin for the Treatment of Early Syphilis, through its STD Clinical Trials Unit. The purpose of this study is to determine whether azithromycin, a drug approved for treatment of other infections, is as effective for syphilis therapy as the usual penicillin treatment. In addition, single-project grants and contracts also support therapeutic evaluations for a number of 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 numerous efforts aimed at developing 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 focused on the development of topical microbicides, which are bactericidal or virucidal intravaginal preparations that would be used by women to prevent STIs.

In September 2000, NIAID convened, with industry, the Summit on Development of Infectious Disease Therapeutics to discuss the state of development of new therapeutics for infectious diseases, including ways in which NIAID could better assist industry and academia in antimicrobial drug development for public health needs. On the basis of recommendations from this meeting, NIAID developed several research initiatives to support the development of vaccines, drugs, and diagnostics for human infectious diseases of public health importance, including diseases caused by NIAID Category A, B, and C agents of bioterrorism. A key component of these initiatives is the development of appropriate partnerships among Government, academia, and the biotechnology, chemical, and pharmaceutical industries.

Division of Allergy, Immunology, and Transplantation

The Division of Allergy, Immunology, and Transplantation (DAIT) supports the research and development of drugs and biologics to treat and prevent immune-mediated diseases. Areas of research include therapeutic approaches to autoimmune diseases, primary immunodeficiencies, asthma and allergic diseases, and rejection of transplanted organs, cells, and tissues, including bone marrow. DAIT established 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 are under way to evaluate new and potentially more effective therapies for asthma and allergic diseases, including immune-based therapies and the development of new agonist or antagonist medications. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to prevent and treat autoimmune diseases. These centers encompass expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes.

Through the Cooperative Clinical Trials in Pediatric Kidney Transplantation, investigators are evaluating a variety of therapies to improve graft survival and to prevent acute and chronic graft rejection. New approaches and therapeutic agents under investigation include monoclonal antibodies in conjunction with standard immunosuppressive therapy, new immunosuppressive drugs to prevent and reverse chronic rejection, pretransplant induction therapies to decrease acute graft rejection and to prevent the onset of chronic rejection, and intravenous gamma globulin to reduce high levels of sensitization among some end-stage renal disease patients, thereby enabling them to become candidates for transplantation.

DAIT, with co-sponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases 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 injurious immune responses and graft rejection while preserving protective immunity to infectious agents. An important aim of ITN is to explore the immune mechanisms underlying efficacy (or lack of efficacy) of candidate drugs. ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, and Europe.

Division of Intramural Research

Much of the research under way in NIAID's Division of Intramural Research (DIR) is aimed ultimately at the development of more effective therapies for infectious and immunologic diseases. DIR's basic studies of the immune system, disease pathogenesis, and microorganism structure, replication, and transmission 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 and integrating genomics and combinatorial chemistry to hone development of second-generation therapeutics based on the same mode of action.
- Studies of mast cells, which initiate and perpetuate allergic inflammation, are identifying key biologic steps in the control of mast cell number and function to identify new approaches, such as cytokine-based therapies, to treat allergic inflammatory diseases.
- To expedite the identification of more effective drugs to treat the transmissible spongiform encephalopathies (TSEs), such as variant Creutzfeldt-Jakob disease (the human disease associated with eating beef contaminated with the "mad cow" disease agent), NIAID scientists developed a high-throughput screening test that can identify compounds that can inhibit the accumulation of the abnormal protein

associated with TSEs. Use of the new test to screen more than 2,000 FDA-approved compounds identified 15 candidate compounds, most of which are known to or are likely to cross the blood-brain barrier and have been administered to humans for other purposes, and which might therefore be effective in either preventing or treating TSEs. Further testing of the candidate inhibitors against scrapie in rodents is under way.[35] For more information on TSEs see page 87.

- NIAID AIDS researchers have designed a new recombinant protein that inhibits HIV binding to the CD4 receptor. The new protein has been engineered to improve on an earlier viral entry inhibitor called soluble CD4, one of the first anti-HIV-1 therapeutics to be tested clinically but which failed to demonstrate clinical efficacy. The new protein appears to have the biochemical properties necessary for efficient inhibition of viral entry and will be tested soon in an animal model.
- In collaboration with investigators at Wyeth, DIR scientists have both identified and determined the mechanism of action of a new class of small molecules that inhibit the growth in cell culture of the varicella-zoster virus, which causes chicken pox and shingles. These small molecules target a different portion of the virus than the currently licensed antivirals and may be more effective.

In addition to these examples of studies under way in the laboratories, 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.