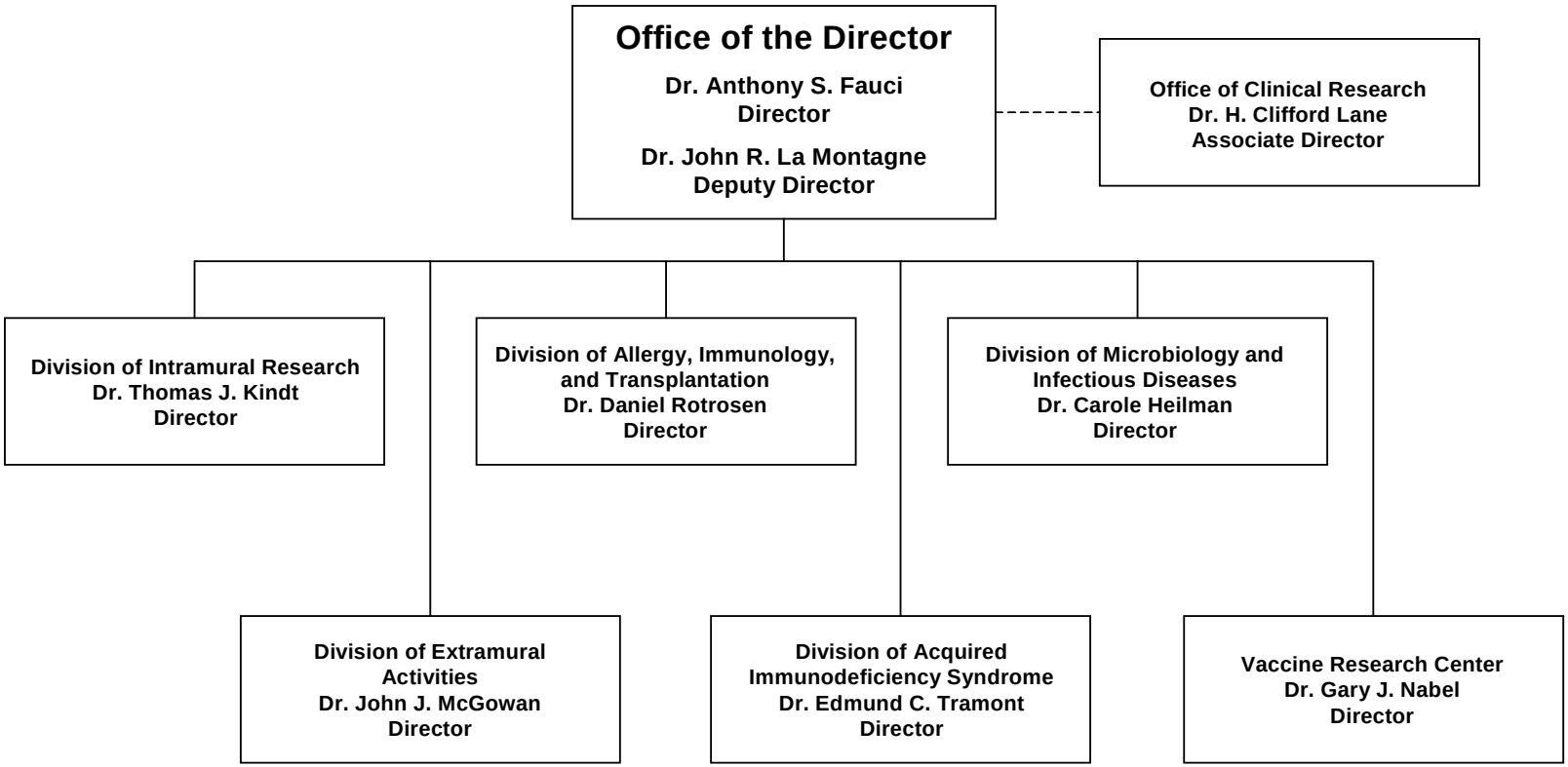
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

National Institutes of Health
National Institute of Allergy and Infectious Diseases
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, [$4,335,155,000] *$4,425,507,000: Provided,* That [$150,000,000] $100,000,000 may be made available to International Assistance Programs, "Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis", to remain available until expended: *Provided further, That up to $150,000,000 shall be for extramural facilities construction grants to enhance the Nations's capability to do research on biological and other agents.*

Language Analysis

Language Provision	*Explanation*
Provided further, That up to $150,000,000, shall be for extramural facilities construction grants to enhance the Nations's capability to do research on biological and other agents.	*Provides authority for NIAID to award extramural construction grants and contracts.*

National Institutes of Health
National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1 /

Source of Funding	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Appropriation	$3,730,973,000	$4,335,155,000	$4,425,507,000
Enacted Rescissions	(24,251,000)	(30,593,000)	---
Subtotal, Adjusted Appropriation	3,706,722,000	4,304,562,000	4,425,507,000
Real transfer to:			
Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	(99,350,000)	(149,115,000)	0
Office of Homeland Security	(583,000)	0	0
Comparative transfer from:			
Fogarty International Center for International Services Branch	113,000	0	0
Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	99,350,000	149,115,000	0
Comparative transfer to:			
NIBIB for Radiology Program	(308,000)	(321,000)	0
Buildings and Facilities	(1,125,000)	(1,201,000)	0
Office of the Director for program changes	(2,123,000)	0	0
Subtotal, adjusted budget authority	3,702,696,000	4,303,040,000	4,425,507,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	3,702,696,000	4,303,040,000	4,425,507,000
Unobligated balance lapsing	0	---	---
Total obligations	3,702,696,000	4,303,040,000	4,425,507,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2003 - $8,958,000; FY 2004 - $9,218,000; FY 2005 - $9,603,000
Excludes $5,407,000 in FY 2003 and $4,237,000 in FY 2004 for royalties.

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTE's	BA	FTE's	BA	FTE's	BA	FTE's	BA
1,387	$3,702,696,000	1,572	$4,303,040,000	1,568	$4,425,507,000	- 4	$122,467,000

This document provides justification for the Fiscal Year 2005 activities of the National Institute of Allergy and Infectious Diseases (NIAID), including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and Biodefense activities. A more detailed description of NIH-wide Fiscal Year 2005 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION AND SUMMARY

The National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), conducts and supports research to understand, treat, and ultimately prevent the myriad of infectious, immunologic, and allergic diseases. For more than 50 years, NIAID-sponsored research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people worldwide.

NIAID's mission is driven by a strong commitment to basic research and the understanding that the fields of immunology, microbiology, and infectious disease are related and complementary. NIAID's research program focuses on biodefense, infectious diseases, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immune-mediated diseases, immune tolerance, and the development of vaccines, therapeutics, and other products.

NIAID-supported research has led to many exciting discoveries, but these discoveries would not have been possible without talented and dedicated scientists and clinicians. NIAID is committed to the support and training of the next generation of biomedical researchers – students just entering graduate school or finishing their doctorates, or established investigators coming in from other fields. NIAID's training and career development awards enable promising scientists to gain education and experience in areas of research critical to the mission of the Institute.

Biodefense: Responding Through Research

The use of deadly pathogens, such as smallpox or anthrax, as agents of bioterrorism is a threat to the civilian population. In the fall of 2001, letters containing anthrax spores were sent through the U.S. mail, resulting in the deaths of five people and 18 confirmed cases of anthrax. Since then, NIAID has strengthened, accelerated, and expanded its biodefense research program to focus on the development of biomedical countermeasures against potential agents of bioterrorism.

NIAID-supported biodefense research includes studies of the pathogenesis of microbes that could be used as weapons, the human immune response to them, and the translation of this knowledge into safe and effective treatments, diagnostics, and vaccines. To achieve its

biodefense research goals, NIAID works closely with partners in academia, industry, and other private and public-sector agencies. NIAID research on organisms and toxins with bioterror potential will enhance understanding of more common and naturally occurring infectious diseases that afflict people here and abroad.

NIAID recognizes that having a cadre of highly trained investigators and clinicians is critical for achieving its biodefense research goals. Biodefense research draws upon the skills, expertise, and commitment of scientists in disparate disciplines, such as bacteriology, virology, immunology, and genomics. NIAID is committed to the training and career development of these scientists.

Confronting Infectious Diseases

Infectious diseases exact a tremendous toll on humankind worldwide. The World Health Organization estimates that over 1,600 people die each hour from an infectious disease, half of whom are children under 5 years of age. Infectious diseases account for 26 percent of total global mortality[1] and are the third leading cause of death in the United States.[2]

Infectious diseases spread without regard to national boundaries, and a local outbreak can rapidly become a global problem, as evidenced by the recent Severe Acute Respiratory Syndrome (SARS) epidemic that spread in a matter of months from China to over 30 countries, including the United States and Canada. HIV/AIDS, which emerged in Africa in the 1970's, has now spread to all corners of the world. Infectious diseases exact a tremendous toll not just on the health of society, but also social and economic development. Indeed HIV/AIDS is now recognized as a threat to global security.

Infectious diseases remain problematic for three reasons: (1) the persistence of intractable infectious diseases such as malaria and tuberculosis; (2) the re-emergence of old infectious diseases such as plague; and (3) the emergence of new infectious diseases such as SARS. NIAID supports basic research to understand how pathogens cause illness and translational research to develop and test vaccines for preventing infections and drugs for treating them. In addition, NIAID supports the development of diagnostics and the establishment of specialized research infrastructure.

Changes in human demographics, behavior, and land use as well as changes in weather patterns, natural disasters, and war contribute to disease emergence and re-emergence by changing transmission dynamics, bringing people into closer and more frequent contact with pathogens. For example, close contact with exotic rodents imported from Africa to the United States as pets was found to be the origin of the recent U.S. outbreak of monkeypox, and the use of exotic civet cats for meat in China may have been the route by which the SARS coronavirus made the transition from animal to human hosts. Furthermore, flood-stricken regions are often plagued by cholera and dysentery outbreaks. Moreover, war can be the catalyst for the spread of diseases to which a population has little or no immunity.

---

[1] The World Health Organization. Communicable Diseases 2002: Global Defence Against the Infectious Disease Threat. Geneva, Switzerland, 2003.

[2] Arias E, Anderson RN, Hsiang-Ching K, Murphy SLm Kochanek KD, Deaths: Final data for 2001. National vital statistics reports 52(3):30-33. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Hyattsville MD, 2003.

NIAID has also made international research a priority. Through investigator-initiated grants and international research networks, NIAID is supporting projects to curtail infectious diseases that primarily affect specific regions of the world (e.g., malaria, leishmaniasis, schistosomiasis, Ebola), as well as diseases that have the potential to cause a global pandemic (e.g., influenza, SARS). As part of its global research agenda, NIAID is working to: target research efforts to develop prevention and therapeutic strategies adapted for the unique needs of developing countries; build and sustain research capacity in-country; stimulate scientific collaboration and global partnerships; and work with in-country scientists to develop training, communications, and outreach programs. NIAID recognizes that a solid foundation of international research and collaborations enhances the U.S. capacity for infectious disease surveillance and the ability to respond to newly emergent disease threats. Moreover, the availability of NIAID-sponsored international study sites for field research, as well as vaccine and drug evaluations against infectious diseases, advance the nation's health agenda and allows for research that might not be possible in the United States.

Confronting HIV/AIDS

Human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS), was first recognized as a global pathogen in the 1980s. Despite recent progress in the treatment and prevention of disease, HIV/AIDS continues to exact an enormous toll worldwide. More than 40 million people worldwide are living with this dreaded disease, and another 30 million have already died from it.[3] In the United States, an estimated 281,931 people were living with HIV/AIDS at the end of 2002, and more than 500,000 people had died from the disease.[4]

NIAID-sponsored researchers have made critical discoveries about the basic biology of HIV and the immune response to HIV infection, which have led to the development of therapies that suppress the growth of the virus in the body. Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication, why the host immune response fails to control the infection, and how reservoirs of virus persist in the body despite highly active antiretroviral treatment. Basic scientific information about how the virus attacks the body and how the body defends itself is critical for identifying additional targets against which therapeutic interventions and vaccines can be directed.

Together, HIV/AIDS, malaria, and tuberculosis (TB) account for more than 5 million deaths each year.[5] In some countries in sub-Saharan Africa, HIV/AIDS, malaria, and TB account for more than half of all deaths. The AIDS pandemic and the resurgence of malaria and TB are impeding the health, economic development, and political stability of many of the world's poorest and most vulnerable countries.

Developing Vaccines and Therapeutics to Protect Human Health

Effective vaccines have contributed enormously to improvements in public health worldwide. Research supported by NIAID has led to new or improved vaccines for a variety of serious diseases, including rabies, meningitis, whooping cough, hepatitis A and B, chickenpox, and

---

[3] World Health Organization. AIDS Epidemic Update, December 2003. Geneva, Switzerland, 2003.

[4] Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report 2002. Vol. 14. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Atlanta, GA, 2003. Available at: http://www.cdc.gov/hiv/stats/hasrlink.htm.

[5] The World Health Organization. Communicable Diseases 2002: Global Defence Against the Infectious Disease Threat. Geneva, Switzerland, 2003.

pneumococcal pneumonia. NIAID is committed to improving global human health through the rigorous pursuit of effective vaccines for human diseases. NIAID has three broad goals in vaccine research: identifying new vaccine candidates to prevent diseases for which no vaccines currently exist; improving the safety and efficacy of existing vaccines; and designing novel vaccine approaches. One important challenge for the 21st century is the development of safe and effective vaccines for three of the greatest microbial killers worldwide: HIV/AIDS, malaria, and tuberculosis.

Understanding Immune Tolerance and Confronting Immune-Mediated Diseases

The past two decades of intensive and highly productive research on the immune system have resulted in a wealth of new information and extraordinary growth in conceptual understanding. These accomplishments now provide realistic opportunities for major advances in the diagnosis, prevention and treatment of a broad range of human diseases involving the immune system. One of the most promising approaches is the induction of immune tolerance. Immune tolerance is the ability of the immune system to recognize and respond to foreign invaders while not reacting harmfully to the body's own tissues. Maintaining tolerance is important, and the loss of tolerance can lead to autoimmune diseases, such as systemic lupus erythematosus and scleroderma. Tolerance induction is also important in preventing the rejection of transplanted organs, tissues, or cells. Based on the more comprehensive knowledge of immune tolerance that is now available, clinical applications to immune-mediated disorders are being developed, and early clinical trials of tolerance induction strategies are already in progress. The potential impact on human health is great, encompassing a wide range of immune-mediated disorders, including: autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus; asthma and allergic diseases; and graft rejection in solid organ, tissue and cell transplantation.

NIAID-supported research focuses on the immune system as it functions in the maintenance of health and as it malfunctions in the production of disease. The immune system is critical to fighting disease, but an inappropriate immune response can unleash an enormous variety of diseases such as allergy and autoimmune disorders.

NIAID-supported research in basic and clinical immunology has led to many promising approaches for treating individuals with immunologic conditions such as multiple sclerosis, type 1 diabetes, and asthma and for preventing the rejection of transplanted organs. Researchers are developing novel ways of selectively blocking inappropriate or destructive immune responses while leaving protective immune responses intact, an area of research known as tolerance induction.

The cause, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases are an important focus of NIAID's research portfolio. Asthma and allergic diseases are among the major causes of illness and disability in the United States. Chronic allergic conditions can significantly decrease the quality of life, patient well-being, employee productivity, and school performance and attendance. The estimated annual health care costs associated with allergic diseases are more than $14 billion. An understanding of the genesis and mechanisms of these diseases will lead to improved diagnostics, treatments, and prevention strategies.

Basic and clinical research in genetics and transplantation are an important part of NIAID's immunology research portfolio. Illnesses such as kidney failure, diabetes, leukemia, end-stage pulmonary disease, cardiovascular disease, and liver disease affect millions of Americans. Transplantation of organs, tissues, or cells can modify outcomes and lifestyles for patients affected by these diseases. Though advances in transplantation have increased the likelihood of

graft acceptance following transplantation, immune-mediated graft rejection and the critical shortage of donor organs remain major challenges in transplantation medicine.

BIODEFENSE: RESPONDING THROUGH RESEARCH

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. Three publications describe the objectives and scope of the NIAID biodefense research agenda: *NIAID Strategic Plan for Biodefense Research*, *NIAID Biodefense Research Agenda for CDC Category A Agents*, and *The NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*.

NIAID researchers have expanded fundamental knowledge about Category A, B, and C Priority Pathogens, the mechanisms by which these agents cause disease, and how infected hosts respond to the microbes. Researchers are using the information to develop safe and effective drugs, vaccines, and state-of-the-art diagnostics. Already, the new findings have contributed to national preparedness against bioterrorist attacks, and have also increased the nation's capability to protect people against the continuous tide of naturally occurring emerging infections such as SARS and West Nile virus.

CATEGORY A AGENTS: DEVELOPMENT OF BIOMEDICAL COUNTERMEASURES AND OTHER RESEARCH PROGRESS

Anthrax

NIAID has accelerated research to develop safer and more effective vaccines against anthrax. In FY 2003, NIAID awarded two contracts to private companies to develop a new anthrax vaccine. Also, NIAID has initiated a Phase I clinical trial of a candidate vaccine based on a recombinant form of anthrax protective antigen (rPA). The anthrax rPA vaccine should stimulate immune responses that prevent anthrax toxins from entering cells and causing disease. Also in FY 2003, NIAID initiated advanced product development of the rPA vaccine. In addition, a cooperative agreement with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), scheduled to begin in 2004, will test whether the course of antibiotic therapy can be decreased by vaccinating subjects with rPA vaccines.

NIAID intramural researchers are continuing a long-term study of those individuals affected and treated in response to the 2001 anthrax attacks to examine the physical effects of anthrax infection and the ability to mount an immune response. Also in FY 2004, NIAID will screen additional FDA-approved antibiotics for efficacy against inhalation anthrax, the most severe form of the disease. Five licensed antibiotics have been selected for the study. The knowledge gained from these efforts could help doctors respond more quickly and effectively in the event of another such attack.

In progress on basic research on anthrax in FY 2003, NIAID-supported researchers reported the sequence of the entire 5.2 million-nucleotide chromosome of the Ames isolate of *Bacillus anthracis*, which is nearly identical to the isolate used in the 2001 attacks, and compared it to the genome sequences of related bacteria. The analysis of the full chromosome sequence of *B. anthracis* indicates that the regulation of gene activity, rather than the presence or absence of specific genes, plays an important role in the bacterium's ability to cause severe disease and death. This information will help scientists better understand the disease-causing capabilities of *B. anthracis*, and to design new vaccines and treatments.

The results of an FY 2003 NIAID intramural study of anthrax lethal toxin in mice suggest that current efforts to design cytokine-suppressing drugs to treat shock in the late stages of disease may be misguided. Previous studies had suggested that anthrax triggers the secretion of large amounts of cytokines, chemical messengers believed to be secreted by specialized immune cells called macrophages in response to *B. anthracis* infection. But the new study shows that tissue damage and death can occur in certain strains of mice even if macrophages are unaffected and no increase in cytokines occurs. Clinicians who treat anthrax patients will need to be aware that the shock associated with anthrax infection may be quite different from that encountered in other bacterial infections.

Smallpox and Other Orthopoxviruses

Smallpox is an acute contagious disease caused by the variola major virus, a member of the orthopox family of viruses. It is among the most dangerous potential biological weapons because the virus easily spreads from person to person, no effective treatment exists, and few people are fully immune to the virus. Previously, NIAID-sponsored clinical trials demonstrated that the existing DryVax smallpox vaccine could be diluted five-fold and retain its potency. Another experimental smallpox vaccine, the Aventis Pasteur Smallpox Vaccine (APSV), is the subject of four NIAID-sponsored extramural trials. Two of these trials were recently completed and analysis of the data collected is ongoing. NIAID is also studying laboratory researchers and other healthcare workers who have received the smallpox vaccine as a routine safety precaution. This study will test improved methods for measuring immune responses to smallpox vaccination, including the production of protective antibodies.

At this time, based in part on NIAID's efforts, the nation has sufficient doses of smallpox vaccine to vaccinate the U.S. population in an emergency. However, the DryVax version of the smallpox vaccine can cause serious adverse reactions, including death, particularly in people whose immune systems are compromised by disease, immunosuppressive drugs, or advanced age. NIAID is vigorously pursuing the development of next-generation smallpox vaccines that are safe and effective for a broad range of civilians, including those who are immunosuppressed. NIAID awarded two contracts in FY 2003 to develop a potential alternative smallpox vaccine, called Modified Vaccinia Ankara (MVA). In FY 2004, NIAID will continue to pursue advanced product development and manufacture of an MVA vaccine. In addition, NIAID has initiated its own studies of the MVA vaccine in intramural laboratories, and is planning similar studies through extramural resources, such as the *Vaccine Treatment and Evaluation Units* (VTEUs). To accommodate an increased number of clinical trials of candidate vaccines against smallpox and other pathogens, NIAID expanded the VTEUs by approximately 60 percent.

In an effort to identify an effective treatment for smallpox infection, NIAID has screened more than 800 compounds for antiviral activity against poxviruses, including the smallpox virus. The most effective to date appears to be cidofovir. NIAID has announced plans to assess the safety and tolerability of an oral form of cidofovir in healthy human volunteers; the trial is scheduled to begin in 2004.

NIAID has also initiated efforts to develop monoclonal antibodies as alternatives to vaccinia immune globulin, a substance used to treat complications caused by the smallpox vaccine. NIAID is establishing the *Atopic Dermatitis and Vaccinia Immunization Network* to develop and implement a research plan to reduce the risk of eczema vaccinatum, a severe and potentially fatal cutaneous dissemination of vaccinia.

In FY 2003, NIAID-supported investigators identified molecular regions (peptides) of two different proteins that are common to the vaccinia and smallpox viruses, and have shown how the human immune system recognizes these peptides. The findings indicate how vaccination

with vaccinia may provide immunity to smallpox, and also could pave the way to the development of safer smallpox vaccines.

NIAID researchers have developed a rapid test for measuring antibodies to vaccinia that can neutralize the virus. The new assay is five- to ten-fold more sensitive than the standard technique, and may also be useful for measuring antibodies against other viruses. Intramural scientists are also determining how orthopoxviruses regulate expression of their genes and replication of their genomes. The new findings may help identify molecular targets for antiviral therapies or vaccines.

Ebola and Other Viral Hemorrhagic Fever Viruses

Ebola virus is a rare, but deadly, microbe that is known to infect only humans and monkeys. Ebola infection, which occurs most often in Africa, causes hemorrhagic fever, characterized by high fever and massive internal bleeding. NIAID researchers at the Vaccine Research Center (VRC) have developed a fast-acting candidate Ebola vaccine that protects monkeys from the virus within one month following immunization. [See "Story of Discovery: Development of a Fast-Acting Ebola Vaccine"] Initial human tests of one component of another Ebola vaccine began in November 2003.

NIAID scientists are continuing to develop a vaccine that would protect against multiple hemorrhagic fever viruses, including Ebola, Marburg, and possibly Lassa virus. If successful, the research would meet a key NIAID objective of developing vaccines that protect against several diseases. Additionally, NIAID scientists have developed a human monoclonal antibody that neutralizes Ebola and protects guinea pigs from a lethal challenge with the Zaire strain of Ebola. The research indicates it is possible to generate antibodies in cell culture that might be useful for passive immunization against Ebola virus infection.

In addition, NIAID researchers have discovered information that may lead to a better understanding of how Ebola causes disease. The scientists found that only three viral proteins are required for capsid assembly, a key life-cycle stage that renders Ebola infectious. The discovery suggests strategies for developing novel therapeutics and vaccines. Researchers also found that the sugar molecules that coat one of the capsid proteins are essential for virus formation, which could lead to the development of antiviral drugs for Ebola hemorrhagic fever.

Story of Discovery

Development of a Fast-Acting Ebola Vaccine

Few viruses are more feared than Ebola virus, a deadly microbe that causes outbreaks in Africa and Asia and kills up to 90 percent of those it infects. Scientists at NIAID's Vaccine Research Center (VRC) recently developed a single dose, fast-acting, experimental Ebola vaccine that successfully protects monkeys from this deadly virus after only one month. If this vaccine proves similarly effective in humans, it may one day allow scientists to quickly contain Ebola outbreaks with ring vaccination – the same strategy successfully used in the eradication of smallpox.

Ebola Virus

Ebola virus and the closely related Marburg virus are the only known members of the filovirus family, one of four distinct virus families that cause viral hemorrhagic fevers. Ebola hemorrhagic fever is characterized by fever, weakness, muscle pain, and headache, followed by vomiting, diarrhea, internal and external bleeding, and often death. Three strains of the Ebola virus – Zaire, Sudan, and Ivory Coast – are highly lethal to humans. The fourth strain, Ebola-Reston, is known to infect, but not cause disease in humans, though it is deadly to monkeys. Ebola virus, along with other viruses that cause hemorrhagic fever, are classified as NIAID Category A Priority Pathogens – microbes considered to pose the greatest risk from intentional exposure. Ebola outbreaks have occurred sporadically since its discovery in 1976, with recent outbreaks occurring in Central Africa. Since the natural reservoir is not known, environmental control and avoidance strategies are impossible. Once a person becomes infected, the virus spreads rapidly to others who come in close contact with the infected person. There is no treatment for Ebola hemorrhagic fever, so an effective vaccine offers the best hope for preventing the disease.

Developing Ebola Vaccines

NIAID VRC scientists have pursued the development of a safe and effective Ebola vaccine for several years. In 2000, they developed an initial candidate vaccine that protects moneys against Ebola virus. Using an immunization strategy called "prime-boost," the researchers combined two different vaccines. The first vaccine, the prime, consisted of strands of DNA containing the gene that encodes Ebola glycoprotein, a protein on the outside of the virus, from each of the three most lethal strains of Ebola virus. The second vaccine, the boost, consisted of a weakened form of a common cold virus called adenovirus, which had been genetically modified to produce Ebola virus glycoprotein. When this prime-boost vaccine was tested in monkeys, all vaccinated animals mounted a strong immune response and survived exposure to a lethal dose of Ebola virus. Though the prime-boost strategy generated potent and lasting immunity in monkeys, administering the vaccine required multiple injections over six months, meaning it would not be effective for containing an outbreak, in which case a fast-acting vaccine would be needed. Human tests of the DNA component of this vaccine began in November 2003.

Building on their previous results, researchers at the NIAID VRC developed a fast-acting candidate Ebola vaccine. While developing the prime-boost vaccine, the scientists had noticed that, in monkeys, a single injection with the modified adenovirus (the boost) produced an immune response against Ebola. Though the magnitude of the response was not as great as that of the prime-boost vaccine, immunity developed rapidly. Working with colleagues at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the VRC scientists tested whether the immune response mounted against the boost would be sufficient to protect monkeys against Ebola infection. The VRC scientists immunized eight monkeys with a single boost injection. The monkeys were then transferred to USAMRIID where they were injected with Ebola virus 28 days after vaccination. All eight animals vaccinated with the boost survived, even those who were challenged with high doses of the virus.

If the new, fast-acting Ebola vaccine proves as effective in clinical trials as in animal tests, it may be just the tool public health officials need to contain naturally occurring outbreaks of Ebola or a terrorist attack with the virus. Even though the single-dose, fast-acting boost vaccine appears to be effective, the initial prime-boost strategy will be important to pursue as well. It elicited a stronger immune response in monkeys and may lead to the development of a vaccine for humans that could protect healthcare workers or others who are at high risk of exposure to the virus.

Sullivan NJ, Sanchez A, Rollin PE, Yang Z-Y, Nabel GJ: Development of a protective vaccine for Ebola virus infection in primates. Nature 408:605-09, 2000.

Sullivan NJ, Gelsbert TW, Gelsbert JB, Xu L, Yang Z-Y, Roederer M, Koup RA, Jahrling PB, and Nabel GJ: Accelerated vaccine for Ebola virus hemorrhagic fever in non-human primates. Nature 424:681-84, 2003.

Dengue Virus

NIAID researchers have developed a live, weakened candidate vaccine against dengue virus, which is carried by mosquitoes and causes millions of cases of dengue fever each year, particularly in children. The virus can also cause dengue hemorrhagic fever, which is lethal approximately 5 percent of the time in most countries. The experimental vaccine, which may be suitable for evaluation in Phase I clinical trials, is chimeric, meaning that the structural genes from one type of dengue virus have been replaced with those of another type.

Botulism

Botulinum toxin, produced by the bacterium *Clostridium botulinum*, is highly lethal, and easy to produce and release into the environment. Exposure to the toxin induces symptoms that include muscle paralysis; difficulty in speaking, swallowing, or seeing; and, in severe cases, the need for mechanical respiration.

NIAID is supporting the development of monoclonal antibody therapies and next-generation vaccines for botulism, which are being assessed in animal models. Also, a *Botulism Research Center* is being funded through the *Food and Waterborne Diseases Integrated Research Network* to broaden the nation's research capacity for developing and testing new treatments for botulism. The network also supports research on the mechanism of action of botulinum toxin in small animal models. The information gained from these studies will allow for improved use of the currently available equine antitoxin botulism therapy, which is effective in reducing the severity of symptoms if administered early in the course of the disease.

Tularemia

Tularemia is caused by the bacterium *Francisella tularensis* and is acquired from direct contact with infected animals or insect bites. Tularemia can also be acquired by aerosolized droplets, the form of the bacterium most likely to be used in an act of terrorism. Symptoms include sudden fever, chills, headache, diarrhea, muscle aches and joint pain, dry cough, and progressive weakness. Tularemia can be fatal if antibiotic therapy fails. A high NIAID priority is the development of a safe and effective vaccine for tularemia.

Previous tularemia vaccines used around the world over the past 50 years have relied on live, weakened strains of *F. tularensis*, including the LVS strain USAMRIID researchers used as the basis of an experimental vaccine. NIAID and USAMRIID have now entered into a collaborative research project to continue the development of a candidate tularemia vaccine. USAMRIID is providing the experimental vaccine and will test its stability. NIAID is performing preclinical studies and will conduct a Phase 1 clinical trial.

Plague

Plague is caused by the bacterium *Yersinia pestis*, which can be aerosolized in large quantities and, in some forms, transmitted easily from person to person. Plague is an international public health concern, and recent outbreaks in human populations in India and Africa have led to its classification as a re-emerging disease. Inhalation of aerosolized *Y. pestis* can cause pneumonic plague which, if left untreated, kills nearly 100 percent of the people it infects. Antibiotics are effective if administered early in the course of disease, but no plague vaccine is available in the United States. The emergence of antibiotic-resistant strains of *Y. pestis* opens the possibility of pneumonic plague epidemics that could not be controlled by standard treatment.

NIAID is supporting the advanced development of candidate vaccines against plague. The vaccines are based on two antigens of *Y. pestis* that appear to play a major role in mediating protective immunity. Additionally, NIAID has completed studies to evaluate a new recombinant plague vaccine, developed by USAMRIID, for its ability to protect mice against flea-borne transmission of the plague bacterium. NIAID has also established a cooperative program with USAMRIID to test FDA-approved antibiotics for efficacy against pneumonic plague in monkeys.

One of the barriers in plague research has been the lack of animal models for studying *Y. pestis* transmission and pathogenesis. NIAID intramural scientists are working to develop rodent models of bubonic and septicemic plague in which the flea-borne route of *Y. pestis* transmission can cause disease. Rodent models for plague should make it possible to investigate the role of specific *Y. pestis* virulence factors, to characterize the host response to naturally acquired infection, and to evaluate new vaccines.

CATEGORY B AND C PRIORITY PATHOGENS: RESEARCH PROGRESS

Many food- and waterborne diseases are caused by Category B and C Priority Pathogens. These include the bacteria *Salmonella*, the O157:H7 strain of *Eschericia coli*, *Ricinus communis* (castor bean, which produces ricin toxin), and the viruses that cause viral encephalitis. The *Food and Waterborne Diseases Integrated Research Network* and *Respiratory Pathogens Research Network* are expanding NIAID's capacity to conduct translational research including the development of diagnostics, vaccines, and therapies as interventions for food- and waterborne and respiratory diseases, including those caused by potential agents of bioterrorism.

NIAID researchers have discovered that today's predominant strains of *Toxoplasma gondii*, a disease-causing protozoan classified as a category B agent, gained the ability to infect nearly all warm-blooded vertebrates about 10,000 years ago through a genetic cross. This study established that parasites like T. gondii can sometimes rapidly adapt to new hosts and present potential new public health threats. Investigators have also found that a simple molecule, called D6R, can block toxins produced by the bacterium *Pseudomonas aeruginosa* in experiments with mice, which may lead to the development of drugs that block diphtheria or anthrax bacterial toxins. Additionally, researchers have discovered that mice can be genetically engineered to produce the human defensin molecule, HD-5, which then protects them from severe illness after oral infection with the food- and waterborne bacterium, *Salmonella*. An exciting possibility that remains to be tested is whether defensin molecules could be used therapeutically to limit intestinal bacterial infections in susceptible individuals or in cases involving intestinal bacteria that are resistant to commonly used antibiotics.

NIAID-funded scientists have sequenced the complete genome of the bacterium that causes Q fever, *Coxiella burnetti*, a category B agent that can cause a debilitating, though rarely fatal, flu-like illness in humans. The researchers have identified genes involved in cell entry, growth, and replication of the bacterium, and the mechanisms it uses to evade host defenses. The information may lead to new targets for vaccines, therapies, and diagnostics against Q fever and other intracellular bacterial infections.

UNDERSTANDING, ASSESSING, AND ENHANCING HOST IMMUNITY

NIAID researchers made discoveries that increase understanding of host immune responses to potential agents of bioterrorism. In one new study, NIAID-supported investigators found evidence for a mechanism by which Ebola and Lassa viruses interfere with the ability of dendritic cells to initiate an adaptive immune response. Dendritic cells occur in tissues throughout the body and present the antigens of pathogens to cells of the immune system to help trigger an immune response. The ability of Ebola and Lassa viruses to suppress immune responses appears to be directed to the cellular pathways responsible for dendritic cell activation, knowledge that may lead to ways to augment immune responses as a strategy to treat and prevent hemorrhagic fever.

In addition, NIAID researchers identified a single protein in mice, called Trif, which acts as a key switch point in frontline immune system responses to both bacterial and viral infections. The finding helps explain why common symptoms, such as fever, occur even with very different types of infection. By understanding how Trif functions, it may be possible to design drugs to inhibit the runaway inflammatory reactions that accompany some infections and immune-mediated diseases.

NIAID continues to broaden and strengthen its research portfolio on understanding and enhancing host immune responses through the *Cooperative Centers for Translational Research on Human Immunology and Biodefense*. Many results obtained in animals translate comparable to humans, but some do not. Therefore, research must also be conducted with human samples to either verify findings or discover the relevant human pathways. This research program includes funding to develop new technologies and make them accessible to researchers, which should help facilitate the translation from animal to human studies, and ultimately facilitate the translation of basic research into clinical applications. NIAID also supports a multi-component grant to create an "encyclopedia" of innate immunity – a comprehensive and detailed picture of the body's essential first line of defense against bacterial, viral, and fungal diseases. This project will enable researchers to develop new ways to study the immune system in living tissue in real time, and provide research materials and information to the scientific community.

Additionally, NIAID is supporting and strengthening the following biodefense-related programs: the *Immune Epitope Database and Analysis Program,* the *Large Scale Antibody and T Cell Epitope Discovery Program,* the *Hyperaccelerated Award/Mechanism in Immunomodulation Trials***,** the *Population Genetic Analysis Program: Immunity to Vaccines and Infections***,** and the *Innate Immune Receptors and Adjuvant Discovery Program*.

DEVELOPMENT OF MEDICAL COUNTERMEASURES AGAINST NUCLEAR/RADIOLOGICAL AND CHEMICAL WEAPONS

The development of safe and effective radiological, nuclear, and chemical countermeasures remains a high priority in national preparedness, and NIAID has begun to examine and develop a research agenda for these areas. In FY 2003, NIAID convened two expert panels in radiobiology and medical chemical defense to identify research gaps. NIAID and the Armed Forces Radiobiology Research Institute (AFRRI) have developed a partnership to promote research endeavors in developing nuclear and radiological countermeasures. In FY 2003, NIAID initiated an Interagency Agreement with AFRRI that led to the procurement of a cobalt-60 gamma radiation source to support future research efforts. In FY 2004, NIAID is expanding this

Interagency Agreement with AFRRI to support research on radioprotectant and radioeliminating drugs, the use of antimicrobial drugs in post-radiation scenarios, and the development of biological assays to quantify radiation exposure.

RESEARCH CENTERS AND OTHER SPECIALIZED RESEARCH FACILITIES

Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases

NIAID awarded funds to establish eight Regional Centers of Excellence (RCE) for Biodefense and Emerging Infectious Diseases Research. This nationwide network of multidisciplinary academic centers will conduct wide-ranging research on infectious diseases and the development of diagnostics, therapeutics, and vaccines. The RCEs will: provide environments in which research on infectious diseases can proceed productively and safely; support investigator-initiated research and training programs; create and maintain critical research resources; and make core facilities available to approved investigators from academia, government, and private industry.

Biocontainment Laboratories

In FY 2003, NIAID announced funding for the construction of two National Biocontainment Laboratories (NBLs) and nine Regional Biocontainment Laboratories (RBLs). The NBLs and RBLs are extramural research facilities that will include state-of-the-art biosafety level 3 (BSL-3) and BSL-4 laboratory facilities in which researchers can study potential agents of bioterrorism as well as naturally occurring infectious diseases in a safe, secure environment. The biosafety laboratories also will be available and prepared to assist national, state, and local public health efforts in the event of a bioterrorism or infectious disease emergency.

Genomics Resources

NIAID has made a significant investment in the genomic sequencing of microorganisms considered agents of bioterrorism. As a result of a coordinated federal effort with the Department of Energy, the Centers for Disease Control and Prevention (CDC), U.S. Department of Agriculture, and the National Science Foundation, and international partners including the Sanger Center, genome sequencing projects are ongoing for at least one strain of every bacterium, virus, or protozoan on the list of Category A, B, and C priority pathogens. In addition, the coordinated federal effort has expanded the sequencing and annotation of variola major viruses. These sequences will be used for identifying potential microbial genetic signatures and targets for the development of drugs and vaccines against these agents.

The NIAID-supported *Pathogen Functional Genomics Resource Center* has developed rigorous protocols and standard operating procedures for high-quality comparative genomic analysis for bacterial genomes, thereby providing standard tools for detecting genetic variation among different strains and clinical isolates. In addition, new genomic software tools have been developed to enhance comparative genomic analyses. NIAID also supports *Microbial Genome Sequencing Centers*, which will allow for rapid and cost-efficient production of high-quality, microbial genome sequences. NIAID also plans to fund the *Biodefense Proteomics Research Program: Identifying Targets for Therapeutic Interventions using Proteomic Technology* in FY 2004 to develop and enhance innovative proteomic technologies and methodologies. The information will increase understanding of the pathogen and host cell proteomes, and facilitate

the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism.

NIAID continues to support the *Orthopoxvirus Genomics and Bioinformatics Resource Center*, a collaborative effort involving four academic centers, CDC, USAMRIID, the Defense Advanced Research Projects Agency, and the American Type Culture Collection. The center includes sequencing and functional comparisons of orthopox genes; it designs and maintains relational databases to store, display, annotate and query genome sequences, structural information, phenotypic data and bibliographic information; and it serves as a repository of well-documented viral strains.

Other Research Resources

NIAID's *Biodefense and Emerging Infections Research Resources Program* supports the acquisition, authentication, storage, and distribution to the scientific community of state-of-the-art research and reference reagents related to biodefense and emerging infectious diseases. The *In Vitro and Animal Models for Emerging Infectious Diseases and Biodefense* program provides a range of resources for preclinical testing of new therapies and vaccines including nonhuman primate models.

FUTURE DIRECTIONS IN BIODEFENSE RESEARCH

NIAID has thus far launched more than 50 initiatives to stimulate biodefense research. NIAID is engaged in a broad effort to develop vaccines against multiple infectious agents. An equally important goal is the development of antibiotics, antivirals, and antitoxins against all classes of biological pathogens. In FY 2005, NIAID will expand support for the *Regional Centers of Excellence; Regional Biocontainment Laboratories; the Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense; and Partnerships for Biodefense.*

In FY 2005, NIAID researchers will continue efforts to obtain the complete genome sequences of potential agents of bioterrorism, and will continue to support the *Microbial Genome Sequencing Centers.* Additionally, NIAID will continue to fund the *Interventions Using Proteomic Technology* initiative, which aims to identify proteins associated with the biology of microbes, host innate and adaptive immune responses, and mechanisms of microbial pathogenesis. NIAID will also continue its support for the *Bioinformatics Integration Support Contract*.

To enhance understanding of immune responses to bioterrorist agents, and to develop immune-based therapies and vaccines NIAID will support several major institute research initiatives: *Modeling Immunity to Emerging/Re-emerging Infectious Diseases, Disabling Innate Immune Invasion: Rational Attenuated Vaccines, and Immune Function and BioDefense in Children, the Elderly and Immunocompromised.*

NIAID researchers will expand and strengthen research on Category A Agents. Researchers will continue to identify organs, tissues, cells, and proteins targeted by anthrax lethal toxin as well as to develop and test small molecule inhibitors of anthrax toxins for use as therapeutic agents. They will also try to understand how the protein capsule that surrounds anthrax spores and a

third anthrax toxin, called edema factor, contribute to disease. Researchers will use the information about anthrax pathogenesis to design improved therapies and vaccines.

Another NIAID goal is to develop more model systems for studying the pathogenesis of orthopoxviruses. The research includes the use of monkeys to study disease progression after monkeypox infection, which is very similar to smallpox in humans. NIAID is also expanding its *in vitro* and *in vivo* systems for screening potential antivirals. And, in a continuing effort to identify new molecular targets for drug and vaccine design, NIAID-funded researchers are analyzing the completely sequenced smallpox virus genome. To date, they have identified five genes whose protein products may be good targets for neutralizing antibodies that could stop smallpox infection.

NIAID will also continue developing safe and effective medical countermeasures for tularemia. A specific initiative is entitled *Development, Testing and Evaluation of Candidate Vaccines Against Tularemia*. Other research, including the development of animal models, is also planned.

CONFRONTING INFECTIOUS DISEASES

MAJOR INTERNATIONAL KILLERS

HIV/AIDS

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). Infection with the virus leads to destruction of a person's immune system, making the infected individual highly susceptible to multiple infections and certain cancers. AIDS is a fatal disorder, and a vaccine is not available to prevent the disease. Treatment with antiviral drug therapy can slow the progression of the disease and decrease associated symptoms. NIAID seeks to increase basic knowledge of the pathogenesis, natural history, and transmission of HIV disease, and to support research that promotes progress in its detection, treatment, and prevention.

Science Advances in HIV/AIDS Research

Rapid Evolution of the Neutralizing Antibody Response to HIV Infection Reveals How the Virus Escapes Immune System Control

Scientists supported by NIAID have discovered a novel mechanism through which HIV escapes from the immune response mounted against the virus. One way that the immune system protects the body from viruses is by producing neutralizing antibodies, which bind to the viral coat protein and prevent the virus from entering and replicating in host cells. During the course of HIV infection, the body produces neutralizing antibodies that recognize and bind to specific regions of the viral envelope protein known as gp120 on the surface of the virus. However, the antibodies fail to eliminate HIV, and this failure is due in part to mutations that occur in the viral genome. Mutations in the *env* gene, which encodes gp120, can render HIV resistant to antibody neutralization. Recently, NIAID-supported scientists analyzed the *env* gene of neutralization-resistant viruses that were isolated from plasma samples of people recently infected with HIV. They observed that *env* mutations did not map to known neutralization regions of the gp120 protein. Instead, the mutations involved changes in sites where multi-sugar molecules, known as glycans, link to gp120. Based on this finding, the scientists proposed a novel mechanism by which HIV is able to escape neutralization – the evolving "glycan shield" mechanism. Changes in the way the glycans are packed can physically block antibodies from gaining access to the neighboring, neutralization regions of gp120. Although the immune system's repertoire of neutralizing antibodies evolves rapidly, a similarly evolving glycan shield allows HIV to escape immune surveillance and persist in the body. Knowledge of how HIV evades the immune system is critical to developing an effective vaccine.

Infection with a Second HIV Strain Possible Despite Potent Immune Response to the Initial Infecting Virus

NIAID-supported researchers have discovered that infection with a second HIV strain is possible even when a potent immune response to the initial infecting virus is mounted. Early antiretroviral therapy given soon after a person is infected with HIV followed by treatment interruption after the immune system has had time to mount an immune response to the virus can slow the progression of the disease. With this type of start-stop therapy, a patient's immune system rebounds enough to keep HIV suppressed for an extended period without medication. NIAID-funded investigators followed a group of patients on start-stop therapy and noted a

sudden increase in the blood level of the virus (breakthrough) in one individual who previously had excellent, prolonged immune control of his original infection. Genetic sequencing of the virus, isolated after the sudden breakthrough, indicated that infection with a second strain of HIV had occurred. The researchers found that even though the immune system could control the original virus, it could not contain the second. This was due to genetic differences in the new virus compared to the original one that decreased recognition by the patient's immune system. The lack of cross-protective immunity for closely related HIV strains has important implications for HIV pathogenesis, treatment, and vaccine development. Given the diversity of existing HIV strains, effective preventatives and therapies will need to be effective against multiple viral strains.

Researchers Identify Class of Potential Antiviral Drugs that Disrupt HIV Structural Core

NIAID-supported scientists are working to develop new and more effective antiviral therapies. NIAID-supported researchers recently identified a novel class of potential antiviral drugs that work by disrupting the HIV capsid, the protein structure that forms a sheath around the HIV genome and is necessary for infection. The researchers used a variety of techniques to identify antiviral compounds that work by blocking the assembly of the HIV capsid. The scientists employed computer models to screen thousands of existing drugs to identify those most likely to bind to the HIV capsid protein and then tested them in the laboratory to determine whether the drugs blocked capsid formation and infection. One compound, called CAP-1, blocked capsid assembly, reduced viral infectivity by 95 percent, and did not appear to be toxic to cultured human immune cells.

Identification of Novel Immune Cell Defects Associated with HIV Disease

NIAID-supported scientists are working to understand immune cell defects commonly associated with HIV infection. Such knowledge may lead to the development of therapies and vaccines to treat or prevent HIV/AIDS. NIAID scientists recently discovered that antibody-producing cells (B cells) of HIV-infected patients who harbor high levels of virus are defective in their responsiveness to stimulation by crucial immune cells called CD4+ T cells or T-helper cells. When T-helper cells are activated in response to a pathogen, they interact with B cells and stimulate them to proliferate and secrete pathogen-specific antibodies that, when bound to their targets, tag invading pathogens for destruction. B cell activation requires direct cellular interaction between B cells and CD4+ T cells as well as growth factors. The researchers found that even though these patients' T-helper cells produced normal amounts of the cell-surface molecule that mediates direct interactions between T cells and B cells, their B cells did not respond properly to T-helper cell stimulation. In addition, the B cells did not respond to interleukin 2 (IL-2), a protein factor produced by T-helper cells which is a second signal necessary for B cell proliferation. The inability of B cells from HIV-infected patients with high levels of virus in their blood to respond to T-helper cell stimulation correlated with decreased amounts of the B cell surface molecule CD25, the receptor that binds IL-2. Interestingly, researchers observed that the expression of CD25 on B cells, as well as their ability to respond to T-helper cell stimulation, was restored when patients reduced their viral burden with antiretroviral drugs. Understanding how the virus interferes with the stimulation of B cells by T-helper cells may provide insights into the inadequacy of the immune response mounted against HIV as well as associated opportunistic infections. In addition, these results may lead to novel strategies for the development of therapeutics and vaccines.

Nevirapine Sustains Advantage Over AZT for Prevention of Mother-to-Child Transmission of HIV-1

NIAID-supported scientists are working to find more effective ways to prevent mother-to-infant transmission of HIV. In a clinical trial sponsored by NIAID, infants who received a single dose of the inexpensive antiviral drug nevirapine (NVP) soon after birth – and whose mothers took one dose of the same drug during labor – were 41 percent less likely to acquire HIV at birth or during breast-feeding than infants in infant/mother pairs who were treated with a multi-dose regimen that included the antiviral drug AZT. In follow-up of study participants, researchers found that the initial advantage gained by infants who, along with their mothers, received one dose of NVP was largely sustained until the children reached 18 months of age, with few serious side effects attributable to NVP. This finding offers compelling new evidence that short-course NVP effectively and safely reduces the HIV infection rate in children born to HIV-positive mothers.

Recent results from experiments conducted by NIAID-supported scientists suggest that treatment with antiretroviral drugs plus vaccination may be effective in decreasing viral load. The scientists hypothesized that administering an HIV/AIDS vaccine during the time when antiretroviral therapy is administered might boost HIV-specific immune responses and lower the viral load. To test their hypothesis, the researchers used rhesus macaque monkeys infected with simian immunodeficiency virus (SIV), a virus closely related to HIV. SIV-infected monkeys on antiretroviral therapy were vaccinated with a weakened poxvirus that had been engineered to make several SIV proteins. When antiretroviral treatment was interrupted, the vaccinated monkeys maintained a lower viral load for at least four months when compared to unvaccinated control animals. During the period SIV was contained, levels of SIV-specific immune cells increased, suggesting that the augmented immune response may have kept the virus in check.

Future Directions in HIV/AIDS Research

In FY 2005, NIAID will continue to support basic and clinical studies that aim to discover and develop new therapies for HIV infection and its complications, and to develop vaccines and other prevention strategies. In addition, NIAID will continue to support a broad array of domestic and international HIV/AIDS research programs that seek to increase basic knowledge of the pathogenesis, natural history, and transmission of HIV disease, and to support research that promotes progress in its detection, treatment, and prevention.

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against most HIV subtypes is the ideal prevention strategy and continues to be one of NIAID's highest priorities. To accelerate vaccine development worldwide, NIAID supports the *HIV Vaccine Trials Network*, which conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate HIV vaccines. NIAID's Vaccine Research Center also conducts HIV vaccine research. To date, NIAID has conducted approximately 67 phase I and II preventive HIV vaccine trials of 38 different products. NIAID continues to work with HVTN to expand capabilities and capacity of existing international sites, as well as to set up new units. Extensive plans are underway in preparation for multiple Phase II trials in multi-site studies that include both U.S. and international units. NIAID is also collaborating with

Department of Defense to initiate a phase III vaccine efficacy trial [using AIDSVAX (B/D)] in Thailand in FY 2004. Extensive time, energy and resources will be invested in infrastructure development, technology transfer and training at new sites.

The *HIV Vaccine Design and Development Teams* encourage the participation of industry, which historically has had greater product development experience. This initiative complements other vaccine development activities by providing an opportunity for talented teams from industry or academia to rapidly advance promising candidates into clinical studies via a focused, milestone-driven, product development-based approach. One of the original teams has already initiated clinical trials of its two vaccines, and the other three original teams are on schedule to have their vaccine products ready for human clinical trial later this year.

Until a highly efficacious vaccine, or even a partially protective vaccine, is developed, control of the epidemic will require a combination of prevention approaches. The *HIV Prevention Trials Network* develops and tests promising nonvaccine strategies to prevent the spread of HIV/AIDS. Clinical trials of topical microbicides and the prophylactic use of antiretroviral drugs to prevent HIV infection are underway.

In FY 2005, NIAID will continue its support of research on candidate therapies and vaccines through several large clinical trials networks. The *Adult Therapeutic Clinical Trials Networks for AIDS* support clinical trials programs in the United States and internationally to address the questions that are of highest priority, from early infection to advanced disease. The *Pediatric AIDS Clinical Trials Group* evaluates treatments for HIV-infected children and adolescents and strategies for preventing mother-to-infant transmission. The *Comprehensive International Program of Research on AIDS* provides long-term support to developing countries to plan and implement a comprehensive HIV/AIDS prevention and treatment research agenda relevant to their populations, and to enhance the infrastructure necessary to conduct such research.

NIAID will continue to support several cohort studies that investigate the epidemiology and natural history of HIV/AIDS in the United States. The *Multicenter AIDS Cohort Study* is an ongoing prospective study of HIV infection in homosexual and bisexual men, both treated and untreated. The *Women and Infants Transmission Study* and *Women's Interagency HIV Study* evaluate the impact of HIV infection on HIV-infected women and their infants.

An important rate-limiting step in basic research is the identification and distribution of state-of-the-art reagents, technology, and standards. In FY 2005, NIAID will continue its support of initiatives aimed at addressing these issues. The *Clinical Research Products Management Center* is a central location for the management of clinical study products for HIV/AIDS clinical trials. The *AIDS Research and Reference Reagent Program* is a worldwide resource of reagents, many of which are not commercially available. The *Virology Quality Assurance Program* serves all NIAID-sponsored HIV/AIDS multi-centered studies, and the *Centers for AIDS Research* provide administrative and shared research support not readily obtained through more traditional funding mechanisms to NIAID-supported projects.

Tuberculosis

One-third of the world's population is infected with the tuberculosis (TB) bacterium *Mycobacterium tuberculosis*.[6] TB is a chronic bacterial infection that is spread through the air, usually infecting the lungs, although other organs are sometimes involved. Most persons that are infected with *M. tuberculosis* harbor the bacterium without symptoms, but many do develop active TB disease. Each year, 8 million people worldwide develop active TB and over 1 million die. Especially alarming is the upsurge in cases of multidrug-resistant tuberculosis.

Science Advances in Tuberculosis Research

Clues About the Survival and Emergence of Drug Resistance in Tuberculosis

NIAID scientists recently discovered clues about the survival and emergence of drug resistance in tuberculosis. A clearer understanding of how TB bacteria acquire drug resistance is essential if the disease is to be controlled. Genetic mutation is one means by which antibiotic-resistant strains of bacteria arise. Researchers used ultraviolet (UV) light to mimic the DNA damage suffered by *M. tuberculosis* as it invaded the host, and then studied how *M. tuberculosis* responded. The researchers determined that *M. tuberculosis* uses an enzyme called a DNA polymerase, DnaE2, to repair its DNA. To learn what role the newly identified enzyme plays in animals, NIAID researchers infected mice with either normal *M. tuberculosis* or *M. tuberculosis* lacking the DnaE2 gene. Mice infected with the normal *M. tuberculosis* died quickly, whereas mice infected with the mutant germ contained the infection more successfully, indicating a role for DnaE2 in helping the bacteria persist in the host's cells. The researchers also used mice to evaluate DnaE2's role in the evolution of drug resistance. They found that mice infected with normal *M. tuberculosis* developed resistance to a common antibiotic, whereas mice infected with strains lacking the DnaE2 gene did not develop antibiotic resistance.

Future Directions in Tuberculosis Research

In FY 2005, NIAID will continue to support basic and clinical TB research, including research on diagnostics, prevention, and treatment, through programs such as the *Tuberculosis Research Unit (TBRU), International Collaborations in Infectious Diseases Research* and the *Millennium Vaccine Initiative – Novel Vaccines for Tuberculosis and Malaria.* NIAID also supports the *Tuberculosis Vaccine Testing and Research Materials* facility, which supplies high-quality, standardized research reagents to investigators worldwide. Multiple clinical trials of therapeutic drugs are ongoing. In addition, a Phase I clinical trial of a candidate TB vaccine is scheduled to be initiated in 2004.

Malaria

Malaria remains one of the major killers of humans worldwide, threatening the lives of more than one-third of the world’s population. It causes an estimated 300 million acute illnesses and

[6] The World Health Organization. Tuberculosis Fact Sheet No. 104. Geneva, Switzerland, 2002. Available from: http://www.who.int/mediacentre/factsheets/who104/en/print.html.

over 1 million deaths each year.[7] Malaria is often cited as a substantial impediment to economic and social development in endemic regions. The threat posed by malaria is increasing as a result of the spread of drug-resistant strains and insecticide-resistant mosquitoes, changing weather patterns, and limitations of the medical and public health infrastructure in many endemic areas.

Science Advances in Malaria Research

Malaria Decoded: Genomic Sequences of Malaria Parasite and Its Mosquito Vector
The genome sequences of *Plasmodium falciparum*, the most lethal malaria-causing parasite, and *Anopheles gambiae*, a mosquito that transmits the parasite to humans, were completed. When information about these genomes is joined with information about the human genome, a much fuller understanding of this disease and its transmission is possible. [See "Story of Discovery: Malaria Decoded: Genomic Sequences of Malaria Parasite and Its Mosquito Vector Completed"]

Future Directions in Malaria Research

In FY 2005, NIAID will continue the systematic implementation of its Research Plan for Malaria Vaccine Development, which was initiated in 1997. NIAID will continue its support for an ongoing clinical trial of a novel candidate malaria vaccine and plans to initiate several additional clinical trials of other candidate vaccines. Malaria vaccine research, development, and clinical evaluation are supported through several mechanisms and include the *Malaria Vaccines: Clinical Research and Trial Preparation Sites*, which will be expanded in FY 2005. NIAID promotes collaborative studies between United States and foreign scientists working in endemic areas through multiple initiatives, including *International Collaborations in Infectious Diseases Research, Tropical Medicine Research Centers*, the *Indo-U.S. Vaccine Action Program*, and the *Multilateral Initiative on Malaria*. NIAID also supports the *NIH Malaria Research and Reference Reagent Resource Center*.

[7] The World Health Organization. Malaria, Fact Sheet No. 94. Geneva, Switzerland. Available from: http://www.who.int/inf-fs/en/fact094.html.

Story of Discovery

Malaria Decoded: Genomic Sequences of Malaria Parasite and Its Mosquito Vector Completed

Despite decades of effort to control malaria, it persists as one of the world's three leading infectious disease killers, together with tuberculosis and AIDS. Malaria kills over one million people each year, most of whom are children in sub-Saharan Africa.[8] In October, 2002, NIAID-funded researchers reported the complete genome sequences of *Plasmodium falciparum*, the parasite species that causes the most severe form of malaria, and of *Anopheles gambiae*, a mosquito species that transmits *P. falciparum.* Obtaining the genome sequences of the malaria parasite and its insect vector, as well as the complete sequence of the human genome, provides the genetic information critical to understanding all stages of the malaria transmission cycle, and offers unprecedented opportunities in the fight against malaria.

An International Effort to Sequence the Genome of the Malaria Parasite

Malaria is most prominent in the tropics and subtropics, regions where the malaria parasite can multiply in the mosquito vectors that carry and transmit it. Left untreated, malaria can cause high fever, chills, severe cramps, vomiting, and diarrhea within 24 hours after infection. Current anti-malarial drugs such as chloroquine are increasingly ineffective because drug-resistant strains of *Plasmodium* have emerged. In 1996, nearly one hundred years after the life cycle of malaria was first discovered, an international consortium of scientists and funding institutions, including the NIH, began a collaboration to determine the genomic sequence of *P. falciparum*. (Three other species of *Plasmodium* also cause malaria in humans – *P. vivax*, *P. malariae*, and *P. ovale* – but *P. falciparum* causes the most lethal form of the disease.) The goals of the consortium were to obtain the complete sequence of *P. falciparum*'s nuclear genome, and ultimately to use the information to develop improved therapies and an effective vaccine for malaria.

Determining the Genomic Sequence of *Plasmodium falciparum*

NIAID-supported investigators and their colleagues analyzed the genome of *P. falciparum*, which consists of 14 chromosomes and includes approximately 5,300 genes. Approximately two-thirds of the proteins encoded by the *P. falciparum* genome appear to be unique to this parasite. Some of the proteins predicted from its genomic sequence enable *P. falciparum* to utilize nutrients from host cells, reproduce inside host cells, evade the immune response, and otherwise survive as an intracellular parasite. Additionally, the sequence data has provided clues about the evolution of the malaria parasite.

Sequencing the Principal Mosquito Vector for Malaria, *Anopheles gambiae*

A. gambiae is the species of mosquito that accounts for the transmission of most cases of malaria. Female *Anopheles* mosquitoes acquire *Plasmodium* when they take a blood meal from an infected host, then transmit the parasite to other hosts at subsequent blood meals. *A. gambiae* has frustrated researchers because of the difficulty of rearing and manipulating the mosquito.

To accelerate efforts to sequence the genome of *A. gambiae* and generate information that could lead to better methods of mosquito control, NIAID, in 1999, joined the *Anopheles Gambiae* Genome Consortium (AGGC). Once underway, the sequencing of the genome of *A. gambiae* took three months. Researchers discovered evidence for approximately 14,000 genes that encode *Anopheles* proteins. They also found unexpected genetic variation in the PEST strain of *A. gambiae*, which may confer important biological differences within the mosquito species. In addition, researchers were able to predict the functions of several *A. gambiae* genes that encode proteins important for digesting a human blood meal.

Using New Knowledge for Public Health

Sequencing the genomes of *P. falciparum* and *A. gambiae* should enable researchers to identify new molecular targets for the design of drugs and vaccines, and to devise new methods to control its insect vector. Scientists have already identified mosquito genes that are similar to genes in other insect species, and are investigating whether previously-validated molecular targets could be used to develop new insecticides, repellents, and irritants.

Gardner MJ et al., Genomic sequence of the human malaria parasite *Plasmodium falciparum.* Nature 419:498-511, 2002.

Holt RA et al., The genome sequence of the malaria mosquito *Anopheles gambiae*. Science 298:129-49, 2002.

[8]The World Health Organization. Communicable Diseases 2002: Global Defence Against the Infectious Disease Threat. G Threat. Geneva, Switzerland, 2003.

Emerging and Re-Emerging Infectious Diseases

The problem posed by emerging and re-emerging infections is one of unparalleled complexity. Many infectious diseases can be expected to increase in incidence or change in distribution under conditions in which currently available control measures prove insufficient; the periodic epidemics of influenza or cholera experienced in the last century provide familiar examples. Research to improve the control of re-emerging pathogens follows established mechanisms, aimed primarily at the discovery and development of new or improved vaccines and therapies. The emergence of new or altered pathogens, occurring through natural evolution or genetic manipulation by bioterrorists, will be unpredictable. NIAID maintains its long-standing commitment to supporting research on emerging and re-emerging diseases with the goal of improving public health.

SARS

In spring 2003, the world became aware of an outbreak of a newly recognized, highly lethal pneumonia that was named severe acute respiratory syndrome or SARS. The outbreak is thought to have originated in southeastern China's Guangdong province in November 2002, with subsequent spread to numerous other countries. SARS quickly became the focus of a worldwide health emergency, forcing quarantines and travel warnings and causing economic damage. As the SARS virus traversed the globe, we were reminded that emerging diseases are a real and present threat. Research is critical to the development of a strategy to confront this global nemesis.

Advances in SARS Research

Finding the Cause of SARS

NIAID's ability to quickly mobilize a team of experts to analyze this previously unknown disease allowed the Institute to rapidly respond. NIAID-supported investigators were the first to report to the World Health Organization the isolation of a virus that was conclusively linked to SARS patients. Researchers obtained clinical specimens from 50 patients with fever, cough, shortness of breath, pneumonia, and a history of close contact to another SARS patient. They inoculated clinical specimens from SARS patients into cell cultures and after 4 days saw that many of the cells were dying – a clear indication of viral infection. The team then used blood samples from these patients to confirm that they had antibodies to this new virus. Using a high-powered microscope, researchers examined a culture from a lung biopsy sample and found virus particles whose surface was studded with an array of proteins resembling a crown around the virus. The researchers used antibody tests and molecular tools to confirm that at least 35 of the patients they were studying were positive for this deadly coronavirus. A simultaneous report identifying the SARS agent as a coronavirus was issued by the CDC.

Live Animal Markets Implicated as Origin of SARS Transmission to Humans

NIAID-supported scientists recently discovered that the live animal markets in China may have been the origin of SARS transmission to humans. NIAID-supported researchers conducting influenza surveillance of live bird markets in Hong Kong expanded their efforts to search animal markets in mainland China for the source of the SARS coronavirus. The researchers collected specimens from more than 25 animals in a live animal retail market in Shenzhen. Genetic tests on the samples confirmed that two animal species, the Himalayan palm civet and the raccoon-dog, were positive for a virus nearly identical to the virus that causes SARS. The civet, the raccoon-dog, and a Chinese ferret badger also had antibodies to the SARS coronavirus.

While researchers do not know if any of these animals is the natural reservoir for SARS, they do know that the live animal markets provide the venue to spread the virus to humans.

The emergence of SARS has resulted in support of a significant number of activities that include animal model development and the production and distribution of research reagents. NIAID has made available several SARS resources and reagents. For example, NIAID-supported the synthesis and distribution of overlapping peptides covering three important genes of the SARS virus that can be used to map the immune responses in exposed and infected people. One application of these tools is to determine if people with different outcomes of infection have a quantitatively different immune response to these viral proteins. In addition, NIAID supported the production and distribution of DNA microchips that contain genetic sequences of the SARS virus. These chips can be used to detect tiny genetic variations between different isolates of the SARS virus. The information derived from experiments using these resources and reagents, coupled with information on the clinical outcomes of patients infected with SARS, will help scientists determine which strains are most dangerous and gain information that may facilitate the development of antiviral drugs and a SARS vaccine. In addition, NIAID is partnering with countries in the Pacific Rim to develop state-of-the-art laboratories that will assist in the event that SARS re-emerges, and that will also provide key resources in the event of a bioterrorist incident.

Future Directions in SARS Research

NIAID research on SARS positions NIAID and the research community to be able to expand SARS research if the virus re-emerges. NIAID supports research aimed at understanding the SARS virus, developing and improving treatment strategies, developing vaccines and other preventive measures, and improving diagnostic tests. In order to accelerate the discovery and development of effective SARS preventatives, therapeutics, and diagnostics, several different development approaches are being undertaken simultaneously. For example, NIAID is supporting the development of an inactivated whole virus vaccine, recombinant vaccines, and subunit vaccines.

In FY 2005, NIAID will continue to support basic and clinical research on emerging diseases through several initiatives, including *Biodefense and Emerging Infectious Disease Research Opportunities* and *Biodefense Proteomics Research Program: Identifying Targets for Therapeutic Interventions Using Proteomic Technology.*

West Nile Virus

West Nile virus (WNV), a member of the family of viruses known as flaviviruses, is spread primarily by infected mosquitoes. The virus was first detected in North America in New York City in 1999, and has spread throughout the continental United States, Canada, and into parts of Mexico and the Caribbean. Most human WNV infections are asymptomatic or mild, though in a small number of cases, the virus can cause life-threatening encephalitis or meningitis. No specific treatment is currently available to treat WNV, and no licensed vaccine is available to prevent the disease.

Scientific Advances in West Nile Virus Research

Development of a Novel Immunoassay that Can Differentiate Natural WNV Infection from Other Flavivirus Infections

In addition to natural transmission of WNV to humans by mosquito bite, it has become clear that

human-to-human transmission of WNV can also occur via blood transfusions, organ donations, and breast feeding, among other routes. The development of a reliable and rapid diagnostic test for WNV that can be used to detect the virus in infected tissues and blood products has been a NIAID priority. The currently-used standardized assay to detect WNV infection lacks the WNV specificity necessary to distinguish it from other related flaviviruses, thus leading to false positive results. NIAID-supported scientists have developed a novel immunoassay that can differentiate WNV infection from other similar flaviviruses. The newly-developed assay, which targets a WNV protein not found in other flaviviruses, substantially improves the specificity of the assay and decreases the frequency of false positive results.

Future Directions in West Nile Virus Research

NIAID will continue its support of ongoing research efforts to develop vaccines, antiviral medicines, and new diagnostic tests for WNV and will continue to support basic research, which is providing new clues about the virus itself, the disease in humans and animals, and how the virus is maintained in the environment.

In FY 2004, NIAID will continue the clinical testing of WNV vaccine candidates, drugs, and other therapeutics, including the recently initiated phase I/II clinical trial to assess the safety, tolerability, and potential efficacy of intravenous immunoglobulin G containing high titers of anti-West Nile virus antibody.

In FY 2005, NIAID will continue to support several WNV initiatives, including *Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics* and *Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases,* and it will launch the new initiative *Modeling Immunity to Emerging/Re-emerging Infectious Diseases*.

Influenza and Other Respiratory Diseases

Infections of the respiratory tract continue to be the leading cause of acute illness worldwide. Upper respiratory infections are very common, especially in children, but seldom have serious or life-threatening complications. Lower respiratory infections include more serious illnesses such as influenza, bronchitis, pertussis (whooping cough), pneumonia, and tuberculosis and are the leading contributor to the 4 million deaths each year caused by respiratory infections.[9]

Influenza epidemics in the United States typically occur between December and March and cause approximately 36,000 deaths each year.[10] In the past, new strains of influenza have emerged to which humans have little or no prior immunity, thus allowing the virus to spread quickly, causing illness and death around the world. Since 1889, at least four major pandemics have occurred. The pandemic of 1918-1919 (often referred to as Spanish Influenza) was one of the worst epidemics of an infectious disease ever recorded, infecting billions and killing 40

[9]The World Health Organization. Communicable Diseases 2002: Global Defence Against the Infectious Disease Threat. Geneva, Switzerland 2003.

[10] Centers for Disease Control and Prevention. Influenza. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Disease Prevention. Atlanta GA, December, 2003. Available from: http://www.cdc.gov/flu/about/disease.htm.

million.[11] This pandemic was followed by others in 1957, 1968, and 1977.

Science Advances in Influenza Research

Development of a Nasal Spray Flu Vaccine

Vaccines have played a major role in the prevention of influenza. NIAID has had a long-standing involvement in the development of a cold-adapted live-attenuated influenza virus vaccine called FluMist, which can be administered intranasally and was approved by the FDA in June 2003. FluMist is based on live influenza viruses that were weakened (attenuated) so they cannot cause the flu. The viruses were selectively grown in the laboratory over many generations at increasingly cooler temperatures. This "cold adaption" is a double safety measure that prevents the viruses from spreading beyond the relatively cool upper respiratory tract. Because the FluMist vaccine contains live virus, it may stimulate a broader immune response than the current vaccine, which contains proteins from inactivated or "killed" viruses.

Future Directions in Influenza and Other Respiratory Diseases Research

NIAID continues to support the Institute's influenza pandemic preparedness initiatives. NIAID-funded investigators are conducting surveillance and characterization of avian influenza viruses with pandemic potential in the live bird markets in Hong Kong. This initiative was expanded in FY 2003 to include additional activities including the establishment of animal influenza surveillance sites in Asia, generating vaccine candidates against influenza strains with pandemic potential, supporting animal surveillance training in the Pacific Rim, and studying the newly emerging influenza strains infecting swine in the United States. In addition, NIAID is supporting several clinical trials of new candidate influenza vaccines.

In FY 2005, NIAID will continue its support for research aimed at more effective diagnosis, prevention, and treatment approaches to control respiratory infections. This includes developing vaccines and treatments for these respiratory illnesses; understanding the long-term health impact respiratory pathogens have in various populations; stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens; and developing better diagnostics. The *Respiratory Pathogen Research Unit* supports pre-clinical and clinical studies to control selected human respiratory pathogens, and the *Respiratory Pathogens Reference Laboratory* supports reagent and assay development for measuring the human immune response to targeted bacterial respiratory pathogens.

Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative diseases such as scrapie of sheep, Creutzfeldt-Jakob disease (CJD) of humans, bovine spongiform ncephalopathy ("mad cow" disease), and chronic wasting disease (CWD) of deer and elk. TSEs are caused by accumulation of prion protein, an abnormal form of a type of protein found normally in humans and animals. The normal physiologic role of prion protein is not fully understood, but transmission of TSE infection causes the transformation of normal prion protein to the TSE form, resulting in disease. Though prion diseases are transmissible, the infectious agent is not fully characterized. How this agent accumulates and causes disease is the subject of intense investigation at NIAID.

---

[11] The World Health Organization. Influenza Fact Sheet No. 211, Geneva, Switzerland, 2003. Available from: http://www.who.int/mediacentre/factsheets/2003/fs211/en/print.html

Research Advances in TSE Research

Subclinical Infection with Mad Cow Agent Possible

Recently, NIAID scientists established that the TSE disease hamster scrapie can cause subclinical disease and jump species, adapting to and causing disease in mice. The scientists studied subclinical TSE-agent infectivity by making four serial passages of hamster scrapie agent in mice. At each step, infectivity was assessed. Replication and adaptation of hamster infectivity in mice was shown in the second year after initial mouse passage. In the third and fourth years, TSEs were found that could infect (1) both hamsters and mice, (2) only mice, and (3) only hamsters. These research results indicate that cross-species infection with transmissible TSEs may lead to subclinical infection and to adaptation of the infection to new species. Results suggest the possibility that humans exposed to mad cow disease or chronic wasting disease, even in the absence of clinical signs, might harbor infectivity which may be able to replicate and adapt over many years to become more dangerous to other humans.

Future Directions in TSE Research

In FY 2005, NIAID will continue research into the fundamental mechanisms of TSE disease and cross-species transmission as well as into the development of diagnostic tests and effective therapies. NIAID research will continue to focus on a number of areas, including understanding how the conversion of the host's normal prion protein to an abnormal form occurs and how it causes disease; further elucidating the mechanisms of cross-species transmission, work that is important in light of the epidemiology of variant CJD as well as the prevalence of CWD in deer and elk herds in the western United States; and investigating the potential use of antibody and other vaccine-based therapies for TSEs.

Hepatitis

In spite of many advances affecting health worldwide, infection, disease, and death from hepatitis viruses are relatively common. Five distinct viruses are known to cause hepatitis, leading to fatigue; jaundice; liver damage; and, in chronic cases, cirrhosis and even liver cancer. Hepatitis A is transmitted by a fecal-oral route, and outbreaks of this acute infectious agent are common at daycare centers, nursing homes, and restaurants. In a recent hepatitis A outbreak, many people became sick, several of whom died, after eating contaminated green onions. Hepatitis B virus and hepatitis C (HCV) virus are blood-borne agents and may cause chronic diseases. Infection with hepatitis D virus is dependent on co-infection with HBV, and may lead to life-threatening superinfections. Hepatitis E virus, like hepatitis A virus, is transmitted via the fecal-oral route and produces an acute illness associated with a high mortality rate in pregnant women.

Science Advances in Hepatitis Research

Hepatitis C Immune Evasion Proteins Uncovered

Through a series of experiments on cells grown in the laboratory, NIAID-supported scientists have discovered one of the strategies HCV uses to evade the immune response. As HCV begins to replicate in its human host, it manufactures enzymes, called proteases, which it requires to transform viral proteins into their functional forms. The researchers determined that one viral protease, NS3/4A, specifically inhibits a key immune system molecule, interferon regulatory factor-3 (IRF-3), which orchestrates a range of antiviral responses. Without this master switch, antiviral responses never begin, and HCV can gain a foothold and persist in its host. Next, the researchers searched for ways to reverse the IRF-3 blockade. They applied a protease inhibitor

to human cells containing modified HCV. This prevented the virus from making functional NS3/4A and restored the cells' IRF-3 pathway. Follow-up studies have shown that, once restored, the immune response reduced viral levels to nearly undetectable levels within days.

Future Directions in Hepatitis Research

In FY 2005, NIAID will continue to support hepatitis research. NIAID will continue to fund the *Hepatitis C Cooperative Research Centers*, which conduct multidisciplinary research on hepatitis C virus, and the *Hepatitis Animal Models* initiative.

OTHER INFECTIOUS DISEASES

Sexually Transmitted Infections

The number of cases of sexually transmitted infections (STIs) has continued to increase dramatically worldwide. More than 25 STIs have now been identified, and each year they affect more than 15 million men and women in the United States.[12] STIs can lead to infertility, tubal pregnancy, cervical cancer, low birth weight, congenital/perinatal infections, other chronic conditions such as neurosyphilis, and increased risk of HIV infection. Treating and preventing STIs have become critical global and national health priorities because of their devastating impact on women and infants and their inter-relationship with HIV/AIDS.

Science Advances in Sexually Transmitted Infections Research

Unusual Bacterium May be the Cause of Reproductive Tract Infections When Other Infections are Ruled Out

NIAID-supported scientists recently discovered that an unusual bacterium may be the cause of many reproductive tract infections in women. Reproductive tract infections, which affect millions of women in the United States every year, are most commonly caused by three microbes: gonococci, chlamydia, and herpes simplex virus. In a significant percentage of cases, the cause of the infection cannot be determined. *Mycoplasma genitalium*, an unusual bacterium that does not have a cell wall and has a genome only slightly larger than that of a virus, is thought to be responsible for some reproductive tract infections of unknown cause in women, since this same organism has been associated with urethritis in men. The NIAID-supported researchers examined specimens collected from patients suffering from infection of the cervix to determine if *M. genitalium* could be the culprit in these infections. The results indicated a significant association of *M. genitalium* with infections of unknown cause of the cervix.

Future Research Directions in Sexually Transmitted Infections Research

NIAID is supporting multiple clinical trials aimed at preventing STIs. A pivotal Phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes in women was initiated in 2002 and is estimated to take four years to complete. This study, which is called the Herpevac Trial for Women, is being conducted as a public-private

[12] Centers for Disease Control and Prevention. Tracing the Hidden Epidemics: Trends in STDs in the Unitied States 2000. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention, Division of Sexually Transmitted Diseases, Atlanta GA, 2001. Available from: http://www.cdc.gov/nchstp/dstd/Stats_Trends/Trends2000.pdf.

partnership.

In FY 2005, NIAID will continue to support research directed toward the understanding, prevention, and control of sexually transmitted infections through the NIAID-funded *Sexually Transmitted Diseases Cooperative Research Centers* and the *Sexually Transmitted Infections Clinical Trials Group* as well as several other related initiatives.

Enteric Diseases

Bacterial and viral infections of the gastrointestinal tract can lead to diarrheal disease as well as other conditions such as ulcers and stomach cancer. Many of these pathogens are transmitted through contaminated food or water. In the United States, diarrhea is the second most common infectious illness, accounting for one of every six (16 percent) of all infectious diseases.[13] Data compiled by the World Health Organization indicate that diarrheal diseases account for 15 to 34 percent of all deaths in some countries and worldwide cause approximately 2 million deaths per year.[14]

Science Advances in Enteric Diseases Research

Helicobacter pylori Cag A Protein Damages Cell-Cell Junctions of the Stomach Lining

Infection with the bacterium *Helicobacter pylori* is a major risk factor for developing peptic ulcer disease, stomach cancer, and primary gastric B-cell lymphoma. Recent studies indicate that over 17,000 cases of stomach cancer occur annually in the United States, resulting in over 12,000 deaths.[15] It is estimated that 50 percent of the world's population is infected with this bacteria.[16] NIAID-funded researchers have identified bacterial and host mechanisms by which *H. pylori* bacteria cause disease. They found that the Cag A protein of *H. pylori* appears to target the specialized attachments between gastric epithelial cells, called tight junctions. By interacting with the host-cell protein ZO-1, which is part of the tight-junction complex, Cag A disrupts the structure of the tight junctions. As a result of the disruption of their tight junctions, gastric epithelial cells no longer function as a protective barrier in the stomach lining. Over time, these molecular and cellular changes may lead to ulcers or even cancer. By discovering a mechanism that allows the *H. pylori* Cag A protein to damage gastric epithelial cells, researchers have identified a potential new therapeutic target for reducing disease associated with *H. pylori* infection.

Future Directions in Enteric Diseases Research

In FY 2005, NIAID will continue to support disease research aimed at understanding, preventing, and treating enteric diseases through multiple Institute initiatives, including *Impact*

---

[13] Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM, and Tauxe RV: Food-Related Illness and Death in the United States. Emerg. Infect. Dis. 5:607-625, 1999.

[14] The World Health Organization. Communicable Diseases 2002: Global Defence Against the Infectious Disease Threat. Geneva, Switzerland, 2003.

[15] U.S. Cancer Statistics Working Group: United States Cancer Statistics: 2000 Incidence. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Atlanta GA, 2003.

[16] Gold, Benjamin D: H. pylori: The Key to Cure for Most Ulcer Patients. U.S. Department of Health and Human Services, Centers for Disease Control, Division of Bacterial and Mycotic Diseases. Atlanta GA, 2002. Available at http://www.cdc.gov/ulcer/keytocure.htm.

of Microbial Interactions on Infectious Diseases; *Food and Waterborne Diseases Integrated Research Network;* and *Biodefense and Emerging Infectious Diseases Research Opportunities.*

Lyme Disease and Other Insect-borne Diseases

Lyme disease is an infection caused by the corkscrew-shaped bacterium *Borrelia burgdorferi* that is transmitted by the bite of deer ticks in north eastern and north central United States and western black-legged ticks in Pacific Coast regions. Lyme disease is the most prevalent tick-borne infectious disease in the United States. The U.S. incidence of reported cases of Lyme disease jumped 40 percent from 2001 to 2002, from 17,029 cases in 2001 to 23,763 cases in 2002.[17]

Science Advances in Lyme Disease Research

Evidence that Post Lyme-Disease Syndrome is not Responsive to Antibiotic Therapy

NIAID-supported scientists are working to find a cure for post Lyme-disease syndrome (PLS). The researchers conducted a clinical trial to examine the effectiveness of antimicrobial therapy in reducing symptoms in patients with Lyme disease with persistent severe fatigue at least six or more months after initial antibiotic therapy. Patients were randomly assigned to receive 28 days of intravenous ceftriaxone or placebo. They then were evaluated for fatigue and/or cognitive function and for spinal fluid infection. Outcomes were assessed after six months. The results indicated that ceftriaxone therapy in patients with PLS with severe fatigue experienced decreased fatigue, but not with an improvement in cognitive function or an experimental laboratory measure of infection.

Future Directions in Lyme Disease Research

In FY 2005, NIAID will continue its long-standing commitment to research on Lyme disease through both intramural and extramural research on animal models of disease; microbial physiology; molecular and cellular mechanisms of pathogenesis; mechanisms of protective immunity; vectors and disease transmission; efficacy of different modes of antibiotic therapy; and the development of more sensitive and reliable diagnostic tests for both early (acute) and late (chronic) Lyme disease. The *Bacteriology and Mycology Biostatistical and Operations Unit* and the *Bacteriology and Mycology Study Group* will continue to support clinical trials aimed at treating Lyme disease.

Fungal Diseases

Severe, sometimes life-threatening, systemic infections caused by fungi have long been recognized in all age groups in all parts of the world. Treatment of these infections now requires prolonged administration of relatively toxic drugs, which are sometimes ineffective even in otherwise healthy patients. Fungal infections are now recognized as a major cause of both morbidity and mortality in patients with an impaired immune system. As the use of immunosuppressive therapies increases in the treatment of patients with malignant and immunologically mediated disease or with organ transplants, the frequency of systemic fungal infections will undoubtedly increase. Mycology and mycology-related research is of crucial importance in solving the serious public health problem posed by fungal infections and is an important component of NIAID's research portfolio.

---

[17] Centers for Disease Control and Prevention, Final 2002 Reports of Notifiable Diseases. MMWR 52:741-750, 2003.

Science Advances in Fungal Diseases Research

Treatment with the Antifungal Medication Itraconazole Prevents Fungal Infections in Children with Chronic Granulomatous Disease

NIAID scientists discovered that the antifungal medication itraconazole is well tolerated and effectively prevents fungal infections in children who have chronic granulomatous disease (CGD), an inherited disorder that leaves individuals prone to frequent severe bacterial and fungal infections. The researchers conducted a clinical trial to evaluate the effectiveness of antifungal prophylaxis. The 39 CGD patients enrolled in the study received a daily dose of either the antifungal drug itraconazole or an inactive look-alike, or placebo. Following the initial random assignment, participants alternated between itraconazole and the placebo annually. The entire study was double-blinded, meaning neither the researchers nor the volunteers knew which drug was being administered at any given time. Over the term of the study, the investigators recorded 12 cases of fungal infection, of which seven were severe and five were mild. When the study was "unblinded," researchers observed that 11 cases of fungal infection occurred in patients who were receiving placebo when the infection arose.

Future Directions in Fungal Diseases Research

In FY 2005, NIAID will support basic and applied mycology research. The *Mycology Research Units* bring together teams of investigators to develop and improve methods for the diagnosis, prevention, and treatment of fungal infections. The *Bacteriology and Mycology Biostatistical and Operations Unit* and the *Bacteriology and Mycology Study Group* continue to support clinical trials against fungal and resistant bacterial infections.

Antimicrobial Resistant Microbes

Antimicrobials have transformed our ability to treat many infectious diseases that were killers only a few decades ago. The increasing use of antimicrobials in humans, animals, and agriculture has resulted in many pathogens developing resistance to these powerful drugs. All major groups of pathogens – viruses, fungi, parasites, and bacteria – can become resistant to antimicrobials. Many diseases are increasingly difficult to treat because of the emergence of drug-resistance, including HIV/AIDS and other viral diseases; bacterial diseases caused by pathogens such as *Staphylococcus aureus* and *Escherichia coli*; respiratory infections, including tuberculosis and influenza; food-borne diseases caused by pathogens such as *Salmonella* and *Campylobacter*; sexually transmitted infections, such as those caused by *Neisseria gonorrhoeae*; fungal infections, such as those caused by *Candida*; and parasitic diseases, including malaria, which is caused by *Plasmodium falciparum*.

Science Advances in Antimicrobial Resistance Research

Understanding How Bacteria Respond to Antimicrobial Agents

NIAID-supported scientists are working to understand at the cellular level how bacteria respond to antimicrobial agents. Multidrug efflux pumps, which are bacterial cell membrane structures, render antimicrobial drugs ineffective by pumping specific drugs out of the cell. An *E. coli* multidrug efflux pump, AcrB, pumps out the widest range of drugs, including penicillin, tetracycline, chloramphenicol, and streptomycin. The researchers used a novel technology to show that drugs are taken up from the thin space between the two outer membrane layers on specific bacteria by a certain region of the AcrB efflux pump. This region seems to determine which drugs will be removed by the pump. The analysis of clinical strains of drug-resistant bacteria showed that overproduction of these pumps is partially responsible for currently

prevalent resistant bacteria.

Future Directions in Antimicrobial Resistance Research

In FY 2005, NIAID will continue to support antimicrobial research, including studies of resistance in fungi, parasites, bacteria, and viruses, through multiple initiatives, including *Innovative Approaches for Combating Antimicrobial Resistance*. NIAID will also continue support for several antimicrobial resistance-related research networks. The *Network on Antimicrobial Resistance in S. aureus* provides bacterial strains to basic and clinical investigators, the *Reservoirs of Antibiotic Resistance Network* collects and makes available information on drug-resistant bacteria, and the *Bacterial and Mycoses Study Group* conducts clinical trials of candidate therapies. Lastly, NIAID will continue to implement the goals outlined by the Interagency Task Force Report for Antimicrobial Resistance

Immune Tolerance

The successful induction of immune tolerance is a major goal for the treatment of many immune-mediated diseases, including asthma and allergic diseases; autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; and rejection of transplanted organs, tissues, and cells. Tolerance-induction approaches selectively block or prevent deleterious immune responses, while leaving protective immunity intact.

Scientific Advances in Immune Tolerance

Reducing Allergy Symptoms with Anti-Allergy Immunotherapy

Preliminary results show that an anti-allergy immunotherapy, known as AIC, administered to study participants prior to the 2001 allergy season resulted in reduced allergy symptoms and other clinical markers of the allergic response through the following 2002 ragweed season, indicating a long-lasting effect of the drug.

Future Directions in Immune Tolerance Research

In FY 2005, NIAID will continue its support for the *Immune Tolerance Network*. This network conducts clinical trials of promising tolerogenic approaches, carries out integrated studies of underlying mechanisms, and develops biomarkers and assays to measure the induction, maintenance, and loss of immune tolerance in humans. NIAID also supports the *Non-Human Primate Immune Tolerance Cooperative Study Group*, which has focused primarily on kidney and islet cell transplantation and will be expanded in FY 2005 to include heart, liver, and lung transplantation research. In addition, NIAID supports the *Innovative Grants on Immune Tolerance* program.

Autoimmune Diseases

Autoimmune diseases are common chronic conditions that involve immune attack of one or more organ systems. These diseases affect approximately 5-8 percent of the United States population and disproportionately afflict women. Examples include type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus. Though great advances have been made in identifying the mechanisms that mediate tissue injury in autoimmune diseases, significant gaps remain in our understanding of what triggers autoimmune diseases and why some people are more susceptible to them than others; the cellular triggers that cause the production of antibodies that react to self tissues, and the chemical mediators of inflammation; and the role of infectious agents and environmental factors in autoimmune disease.

Science Advances in Autoimmune Diseases Research

A Novel Function of Immunoglobulins

NIAID-supported scientists recently discovered a novel function of intravenous immunoglobulin (IVIG), a type of antibody that aids in fighting infection. IVIG is used to treat a range of autoimmune diseases and other inflammatory conditions. NIAID-supported scientists discovered that high doses of IVIG work by attaching to certain proteins of the complement system, a large group of proteins in the blood which act together to coordinate an immune system attack against molecules recognized as foreign, thus preventing the binding of IVIG to complement. This binding stops the various immune responses that are normally triggered when complement is activated. This discovery represents a novel function for immunoglobulins and

helps explain the anti-inflammatory effects of IVIG and may expand its clinical application.

Future Directions in Autoimmune Diseases Research

In FY 2005, NIAID will support a broad range of basic and clinical research programs in autoimmunity. The *Autoimmunity Centers of Excellence* support collaborative basic and clinical research, including clinical trials of immunomodulatory therapies. This initiative will be renewed and expanded in FY 2005. The *Autoimmune Diseases Prevention Centers* conduct basic research on the development of new targets and approaches to prevent autoimmune diseases and to evaluate these approaches in pilot and clinical studies. NIAID also supports the *Multiple Autoimmune Diseases Genetics Consortium* (MADGC), a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more autoimmune diseases.

Asthma and Allergic Diseases

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States, affecting as many as 40 to 50 million Americans. The immune system functions as the body's defense against invading bacteria and viruses. In most allergic reactions, however, the immune system responds inappropriately to generally harmless molecules by producing allergic antibodies. These antibodies, called IgE antibodies, initiate allergic inflammation, rhinitis, and asthma.

Scientific Advances in Asthma and Allergic Diseases Research

Exposure to Pets in Infancy Prevents Many Allergies Later in Life

Many studies have attempted to elucidate the relationship between environmental exposures, especially during infancy, and the risk of allergic sensitivity later in life. NIAID-supported investigators discovered that children raised in a home with two or more cats or dogs during the first year of life were, at ages 6 to 7, less likely to develop allergic antibodies to pets than children raised in homes without pets. In addition, the children with pets had a substantially decreased risk of developing IgE antibodies to dust mites, mold, ragweed pollen, and grass. The researchers observed that 34 percent of children without exposure to dogs or cats in the first year of life were sensitized to at least one allergen, compared to only 15 percent of children exposed to two or more cats or dogs. Identifying the mechanisms through which exposure to pets early in life inhibits the development of IgE antibodies to a wide variety of allergens may lead to new strategies for preventing allergic diseases and asthma.

Reducing Asthma Severity and Health Care Utilization in Inner-City Children

In collaboration with NIAID intramural scientists, NIAID-funded scientists have translated the asthma risk assessment tool developed and validated by the NIAID National Cooperative Inner City Asthma Study into a simplified web-based form (Child Asthma Risk Assessment Tool, CARAT). This will be made available through the NIAID web site along with a linked repository of instructional materials and references related to the NCICAS intervention. This interactive resource will enable caregivers of children with asthma to use the CARAT to identify asthma risk factors specific to their child and will provide an action plan of steps that can be taken to minimize the impact of those factors on their child's asthma. The CARAT is designed to complement traditional physician-directed asthma management plans and will facilitate the dissemination of key elements of the NCICAS intervention to a very large, medically underserved population.

Future Directions in Asthma and Allergic Diseases Research

In FY 2005, NIAID will continue to support basic and clinical asthma and allergic diseases research. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of allergic diseases represent a major focus of NIAID's basic and clinical research portfolio. NIAID'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. A new initiative, *Immunobiology of Acute Asthma*, seeks to stimulate research on the cellular and molecular mechanisms that lead to airway obstruction during asthma attacks. The *Inner City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity*, launched in FY 2002, is a network of basic scientists and clinical investigators who are evaluating the efficacy of promising immune-based therapies for reducing asthma severity and preventing onset in inner-city children.

Transplantation

The principal goal of transplantation is the physical and functional replacement of failing organs and tissues. The most striking advances in transplantation have come in the past 30 years, with improvements in surgical techniques and the development of immunosuppressive agents to inhibit the recipient's immune responses against the graft. These advances have made transplantation the preferred treatment for many end-stage organ diseases. Today, transplantation procedures are performed using more than 25 different organs and tissues, with one-year graft survival rates often exceeding 80 percent. However, two major impediments to successful transplantation remain: immune-mediated graft rejection and the critical shortage of donor organs. Despite the improvements in one-year graft survival rates for all organs, long-term graft survival rates have not significantly improved. Availability of organ donors remains a limiting factor to transplantation in the United States. NIAID-supported research on the genetic factors associated with graft survival has provided valuable insights into the relative risk for graft failure. The NIAID is committed to understanding the genetic basis of the immune response to transplanted organs and tissues.

Science Advances in Transplantation Research

Pancreatic Islet Cell Transplantation Holds Promise as Cure for Type 1 Diabetes

Pancreatic islet cell transplantation holds considerable promise as a cure for type 1 diabetes, an autoimmune disease in which the insulin-producing islet cells of the pancreas are destroyed. However, transplanted islets are also subject to destruction by specialized immune system cells call CD8+ T cells. NIAID-supported investigators have identified a critical role for CD103, a molecule found on a subpopulation of CD8+ T cells, which allows these T cells to enter and/or be retained in islet grafts. The researchers found that CD103 binds to a receptor protein, E cadherin, on the surface of a variety of cells, such as pancreatic islets and kidney renal tubules. Using genetically modified mice that lack CD103, these researchers found that potentially destructive CD8+ T cells do not enter the islet graft. Furthermore, the majority of these mice, which were made diabetic before islet transplantation, did not reject their islet grafts and maintained normal blood glucose levels indefinitely. These studies suggest that CD103 may be a therapeutic target to prevent rejection of transplanted pancreatic islets.

Future Directions in Transplantation Research

In FY 2005, NIAID will continue its support for transplantation research. The *Non-Human Primate Immune Tolerance Cooperative Study Group* supports evaluation of the safety and

efficacy of novel tolerance-induction mechanisms in non-human primate models and is focused primarily on kidney and islet cell transplantation. This initiative will be expanded in FY 2005 to include heart, liver, and lung transplantation research. Two new initiatives seek to better understand the critical factors that mediate the immune responses to transplanted tissues and cells. The *Human Leukocyte Antigen Genetics in Infectious and Immune-mediated Diseases* initiative will support the characterization of the genes that control the immune response to transplanted tissues, pathogens, and tumors; and the *Immunobiology of Xenotransplantation* initiative will address the shortage of organs by supporting research to develop safe and effective strategies for organ and tissue transplantation across species barriers.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases are caused by intrinsic defects in the cells of the immune system and are often due to inherited genetic defects. This is in contrast to secondary immunodeficiency diseases, which are due to another illness or infection, such as HIV. The hallmark of primary immunodeficiency diseases is increased susceptibility to infection, but these disorders are associated with other immune diseases, such as autoimmune phenomena, certain types of anemia, arthritis, diarrhea, and certain malignancies of the immune system. Approximately 500,000 Americans are afflicted with primary immunodeficiencies, 5,000 to 10,000 of whom are severely affected. In addition, it is estimated that approximately 500,000 additional persons remain undiagnosed.

Science Advances in Primary Immunodeficiency Diseases

Thymus Transplantation Restores Immune System Function in Complete DiGeorge Syndrome
DiGeorge syndrome is a congenital primary immunodeficiency disorder in which the thymus gland, heart, and parathyroid glands fail to develop normally. People with complete DiGeorge syndrome, which is 100 percent fatal by three years of age, have no thymus, the organ located in the upper chest cavity which is required for the normal development of white blood cells. NIAID-supported researchers found that transplantation of thymus tissue is an effective and well-tolerated treatment for complete DiGeorge syndrome. The researchers conducted a Phase I clinical trial in which 12 infants with complete DiGeorge syndrome received transplants of thymus tissue obtained from infants who had undergone corrective cardiac surgery requiring partial removal of a normal thymus. Seven patients survived (58 percent), were well 15 months to 8.5 years following the transplantation, and had increased immune function. The five patients who did not survive died of a range of congenital problems. Follow-up studies will determine whether the surviving children eventually develop normal immune response levels, and further study of these patients may help unravel the processes by which the thymus supports immune cell maturation and the development of protective immunity.

Future Directions in Research on Primary Immunodeficiency Diseases

In FY 2005, NIAID will continue its support for the *Primary Immunodeficiency Diseases Consortium*, a coalition of the world's most prominent researchers in the field of primary immunodeficiency diseases that is working to prioritize and coordinate future research directions and develop new resources for the study of these comparatively rare disorders. In addition, NIAID will continue to support research for the development large animal models of primary immunodeficiency diseases as well as clinical trials to determine the most efficacious bone marrow transplantation regimen in patients with these diseases.

NIH ROADMAP: ACCELERATING MEDICAL RESEARCH PROGRESS

The aim of the NIH Roadmap is to promote the efficient and effective movement of discoveries from bench to bedside. NIAID's scientific mission will be advanced by information, reagents, technology, and infrastructure produced by NIH Roadmap initiatives. For example:

- The *Re-engineering the Clinical Research Enterprise* Roadmap initiative aims to improve communication among the academic centers, community-based physicians and patient advocacy alliances involved in clinical research; develop new technologies to help scientists better understand the impact of new interventions on health status; help expand and enhance the clinical research workforce; and will facilitate access to standardized data and regulatory requirements. These efforts will advance NIAID's goal of rapidly moving scientific advances from the laboratory into the clinical practice; enable NIAID to better direct research on therapies that would be most highly valued by patients; and help NIAID ensure that talented investigators, including those from diverse backgrounds, enter immunology and infectious diseases research. The initiative will also improve the efficiency of NIAID-funded researchers by reducing duplication and unnecessary overlap between trials.

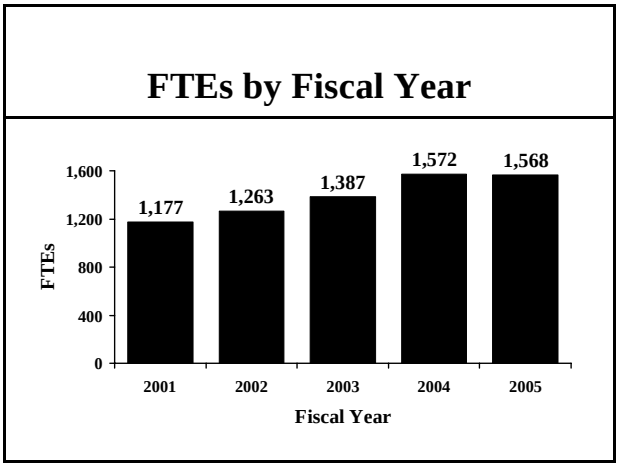
- The goal of NIH Roadmap initiative *Building Blocks, Biological Pathways, and Networks* is to facilitate the development of the next generation of tools and technologies needed to better understand the array of intricate and interconnected pathways that facilitate communication among genes, molecules, and cells. These next-generation tools and technologies will advance NIAID's initiatives aimed at understanding the biology of microbes, pathogenesis, infectivity, and host response, as well as efforts aimed at developing new drugs, vaccines, and diagnostics.

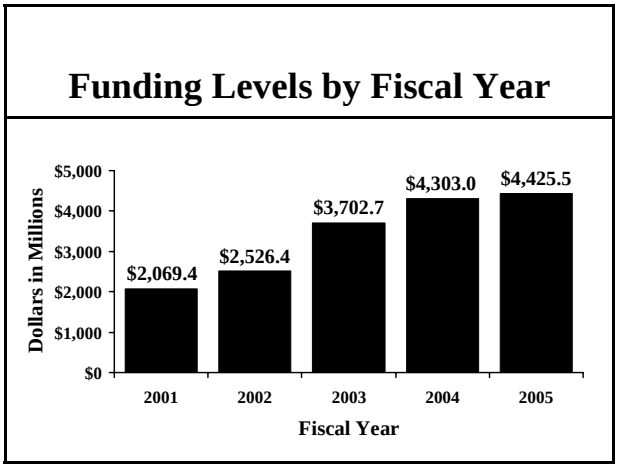
- The *Molecular Libraries and Molecular Imaging* Roadmap initiative aims to provide scientists with access to a large number of small molecules that can be used as chemical probes to study biological pathways in greater depth. In addition, the availability of these compounds will facilitate the development of new drugs. The large number of small molecules made available by the *Molecular Libraries and Molecular Imaging* initiative will advance NIAID's translation of basic research findings into novel therapeutics and prevention strategies for immune-mediated diseases, HIV/AIDS, emerging infectious diseases, and vaccines.

Budget Policy

The Fiscal Year 2005 budget request for the NIAID is $4,425,507,000, including AIDS and Biodefense, an increase of $122,467,000 and 2.8 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NIAID's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five-year history of FTEs and Funding Levels for NIAID are shown in the graphs below. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.





NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. The NIAID is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NIAID will support 1,319 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 40 research centers, 405 other research grants, including 346 clinical career awards, and 258 R&D contracts. Intramural Research and Research Management and Support receive 8.1 percent and 6.1 percent, respectively, over FY 2004. The additional increases in these areas are the result of conducting and supporting biodefense research.

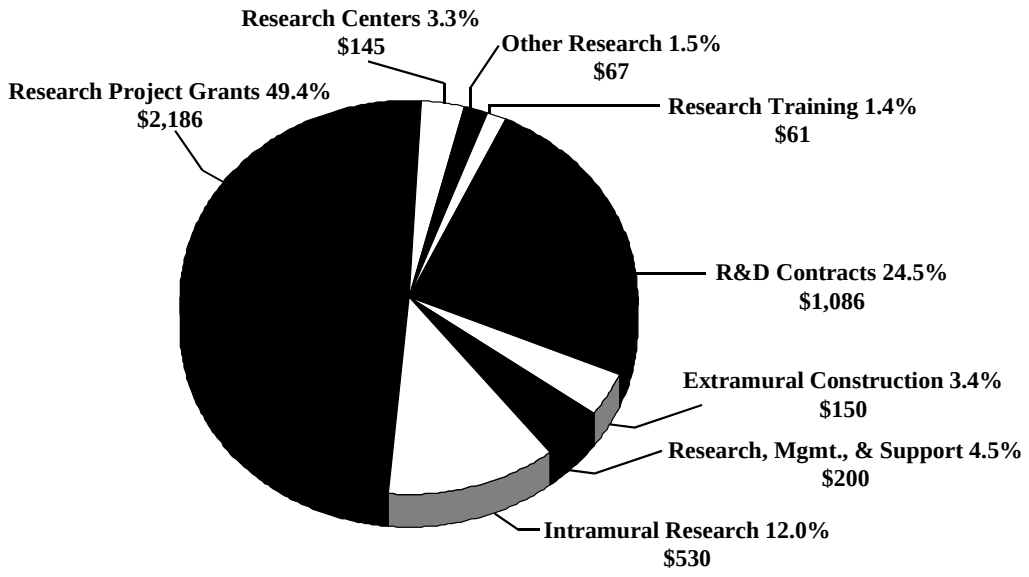
Included as part of the increase for NIAID in FY 2005 is $41,000,000 to support the

development of an HIV/AIDS vaccine. An HIV/AIDS vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against most HIV subtypes is the ideal prevention strategy and continues to be one of NIAID's highest priorities. Additionally, the 15.2 percent decrease in Research and Development Contracts is mainly due to reductions of $50,000,000 for the Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis, and $120,000,000 for next-generation anthrax vaccine. NIAID resources that were programmed in FY 2004 to support advanced development of the next-generation anthrax vaccine will become available in FY 2005 for other critical research activities. These resources will allow the biodefense program to stay on track to meet its major long-range goals as identified in the strategic plan for biodefense research, such as the construction of crucial biosafety labs and the development of animal models to test the effectiveness of potential vaccines, drugs and diagnostics. These funds will also permit NIAID to increase support for the research and development of other biodefense countermeasures.

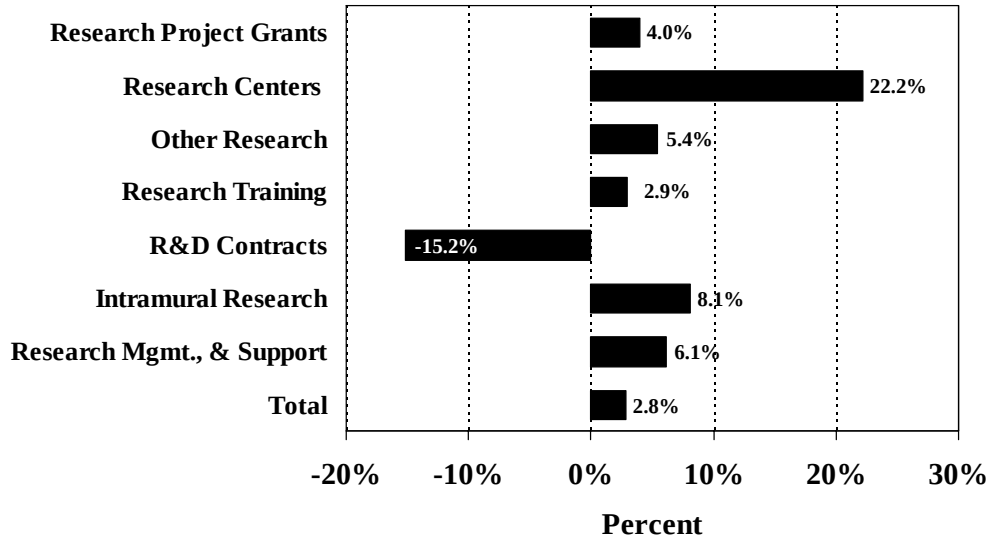
The mechanism distribution by dollars and percent change are displayed below:

FY 2005 Budget Mechanism

Dollars in Millions



FY 2005 Estimate
Percent Change from FY 2004 by Mechanism



NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Mechanism - Total

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,691	$1,269,680,000	2,931	$1,384,464,000	3,450	$1,597,132,000
Administrative supplements	(83)	16,387,000	(76)	14,437,000	(78)	14,805,000
Full funded	18	2,411,000	50	84,909,000	34	42,924,000
Single year	1,260	399,839,000	1,574	521,702,000	1,300	433,568,000
Renewal	350	114,924,000	434	156,698,000	362	125,177,000
New	908	284,433,000	1,138	364,522,000	936	307,881,000
Supplements	2	482,000	2	482,000	2	510,000
Subtotal, competing	1,278	402,250,000	1,624	606,611,000	1,334	476,492,000
Subtotal, RPGs	3,969	1,688,317,000	4,555	2,005,512,000	4,784	2,088,429,000
SBIR/STTR	247	69,314,000	342	95,794,000	347	97,536,000
Subtotal, RPGs	4,216	1,757,631,000	4,897	2,101,306,000	5,131	2,185,965,000
Research Centers:						
Specialized/comprehensive	33	62,729,000	37	112,066,000	40	137,357,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	1,500,000	3	3,274,000	0	4,308,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	3,199,000	0	3,180,000	0	3,221,000
Subtotal, Centers	33	67,428,000	40	118,520,000	40	144,886,000
Other Research:						
Research careers	286	33,914,000	329	40,532,000	346	42,559,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	2,323,000	1	1,634,000	1	1,657,000
Minority biomedical research support	0	1,051,000	0	1,074,000	0	1,088,000
Other	51	19,589,000	3	20,563,000	58	21,914,000
Subtotal, Other Research	337	56,877,000	333	63,803,000	405	67,218,000
Total Research Grants	4,586	1,881,936,000	5,270	2,283,629,000	5,576	2,398,069,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	184	7,722,000	196	8,538,000	196	8,538,000
Institutional awards	1,016	46,345,000	1,090	51,103,000	1,123	52,847,000
Total, Training	1,200	54,067,000	1,286	59,641,000	1,319	61,385,000
Research & development contracts	238	787,111,000	248	1,280,491,000	258	1,085,554,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	752	451,057,000	749	490,639,000	749	530,337,000
Research management and support	635	155,963,000	823	188,640,000	819	200,162,000
Cancer prevention & control	0	0	0	0	0	0
Construction		372,562,000		0		150,000,000
Total, NIAID	1,387	3,702,696,000	1,572	4,303,040,000	1,568	4,425,507,000
(RoadMap Support)		(0)		(14,267,000)		(27,882,000)
(Clinical Trials)		(582,743,000)		(662,877,000)		(724,434,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2003 Actual FTEs	FY 2003 Actual Amount	FY 2004 Final Conference FTEs	FY 2004 Final Conference Amount	FY 2005 Estimate FTEs	FY 2005 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Allergy, Immunology, and Infectious Diseases		$3,095,676		$3,623,761		$3,695,008		$71,247
Subtotal, Extramural research		3,095,676		3,623,761		3,695,008		71,247
Intramural research	752	451,057	749	490,639	749	530,337	0	39,698
Res. management & support	635	155,963	823	188,640	819	200,162	(4)	11,522
Total	1,387	3,702,696	1,572	4,303,040	1,568	4,425,507	(4)	122,467

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Summary of Changes

FY 2004 Final Conference				$4,303,040,000
FY 2005 Estimated Budget Authority				4,425,507,000
Net change				122,467,000
	FY 2004 Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$86,850,000		$1,219,000
b. Annualization of January 2004 pay increase		86,850,000		903,000
c. January 2005 pay increase		86,850,000		1,001,000
d. One less day of pay		86,850,000		(332,000)
e. Payment for centrally furnished services		66,796,000		2,004,000
f. Increased cost of laboratory supplies, materials, and other expenses		336,993,000		34,903,000
Subtotal				39,698,000
2. Research Management and Support:				
a. Within grade increase		85,877,000		1,438,000
b. Annualization of January 2004 pay increase		85,877,000		895,000
c. January 2005 pay increase		85,877,000		992,000
d. One less day of pay		85,877,000		(329,000)
e. Payment for centrally furnished services		23,000,000		690,000
f. Increased cost of laboratory supplies, materials, and other expenses		79,763,000		7,836,000
Subtotal				11,522,000
Subtotal, Built-in				51,220,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Summary of Changes--continued

CHANGES	FY 2004 Budget Base No.	FY 2004 Budget Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,931	$1,398,901,000	519	$213,036,000
b. Competing	1,624	606,611,000	(290)	(130,119,000)
c. SBIR/STTR	342	95,794,000	5	1,742,000
Total	4,897	2,101,306,000	234	84,659,000
2. Research centers	40	118,520,000	0	26,366,000
3. Other research	333	63,803,000	72	3,415,000
4. Research training	1,286	59,641,000	33	1,744,000
5. Research and development contracts	248	1,280,491,000	10	(194,937,000)
Subtotal, extramural				(78,753,000)
	FTEs		FTEs	
6. Intramural research	749	490,639,000	0	39,698,000
7. Research management and support	823	188,640,000	(4)	11,522,000
8. Construction		0		150,000,000
Subtotal, program		4,114,400,000		122,467,000
Total changes	1,572		-4	122,467,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Budget Authority by Object

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	1,572	1,568	(4)
Full-time equivalent of overtime & holiday hours	5	5	0
Average ES salary	$0	$0	$0
Average GM/GS grade	11.1	11.1	0.0
Average GM/GS salary	$70,324	$72,715	$2,391
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$76,497	$79,098	$2,601
Average salary of ungraded positions	97,707	101,029	3,322

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$73,779,000	$76,214,000	$2,435,000
11.3 Other than Full-Time Permanent	41,775,000	43,154,000	1,379,000
11.5 Other Personnel Compensation	4,369,000	4,513,000	144,000
11.7 Military Personnel	5,686,000	5,874,000	188,000
11.8 Special Personnel Services Payments	13,605,000	14,054,000	449,000
Total, Personnel Compensation	139,214,000	143,809,000	4,595,000
12.1 Civilian Personnel Benefits	32,055,000	33,113,000	1,058,000
12.2 Military Personnel Benefits	1,420,000	1,467,000	47,000
13.0 Benefits for Former Personnel	38,000	39,000	1,000
Subtotal, Pay Costs	**172,727,000**	**178,428,000**	**5,701,000**
21.0 Travel & Transportation of Persons	6,842,000	7,409,000	567,000
22.0 Transportation of Things	1,107,000	1,146,000	39,000
23.1 Rental Payments to GSA	3,286,000	3,384,000	98,000
23.2 Rental Payments to Others	2,117,000	2,326,000	209,000
23.3 Communications, Utilities & Miscellaneous Charges	4,302,000	4,672,000	370,000
24.0 Printing & Reproduction	791,000	831,000	40,000
25.1 Consulting Services	1,183,000	1,304,000	121,000
25.2 Other Services	132,191,000	145,488,000	13,297,000
25.3 Purchase of Goods & Services from Government Accounts	362,049,000	385,863,000	23,814,000
25.4 Operation & Maintenance of Facilities	45,152,000	48,748,000	3,596,000
25.5 Research & Development Contracts	1,154,637,000	958,931,000	(195,706,000)
25.6 Medical Care	2,242,000	2,369,000	127,000
25.7 Operation & Maintenance of Equipment	4,869,000	5,158,000	289,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**1,702,323,000**	**1,547,861,000**	**(154,462,000)**
26.0 Supplies & Materials	38,288,000	39,783,000	1,495,000
31.0 Equipment	27,945,000	30,171,000	2,226,000
32.0 Land and Structures	16,000	16,000	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	2,343,270,000	2,609,454,000	266,184,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	26,000	26,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**4,130,313,000**	**4,247,079,000**	**116,766,000**
Total Budget Authority by Object	**4,303,040,000**	**4,425,507,000**	**122,467,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	73,779,000	76,214,000	2,435,000
Other Than Full-Time Permanent (11.3)	41,775,000	43,154,000	1,379,000
Other Personnel Compensation (11.5)	4,369,000	4,513,000	144,000
Military Personnel (11.7)	5,686,000	5,874,000	188,000
Special Personnel Services Payments (11.8)	13,605,000	14,054,000	449,000
Total Personnel Compensation (11.9)	**139,214,000**	**143,809,000**	**4,595,000**
Civilian Personnel Benefits (12.1)	32,055,000	33,113,000	1,058,000
Military Personnel Benefits (12.2)	1,420,000	1,467,000	47,000
Benefits to Former Personnel (13.0)	38,000	39,000	1,000
Subtotal, Pay Costs	**172,727,000**	**178,428,000**	**5,701,000**
Travel (21.0)	6,842,000	7,409,000	567,000
Transportation of Things (22.0)	1,107,000	1,146,000	39,000
Rental Payments to Others (23.2)	2,117,000	2,326,000	209,000
Communications, Utilities and Miscellaneous Charges (23.3)	4,302,000	4,672,000	370,000
Printing and Reproduction (24.0)	791,000	831,000	40,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	733,000	823,000	90,000
Other Services (25.2)	132,191,000	145,488,000	13,297,000
Purchases from Govt. Accounts (25.3)	132,484,000	149,547,000	17,063,000
Operation & Maintenance of Facilities (25.4)	45,152,000	48,748,000	3,596,000
Operation & Maintenance of Equipment (25.7)	4,869,000	5,158,000	289,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**315,429,000**	**349,764,000**	**34,335,000**
Supplies and Materials (26.0)	38,241,000	39,731,000	1,490,000
Subtotal, Non-Pay Costs	368,829,000	405,879,000	37,050,000
Total, Administrative Costs	**541,556,000**	**584,307,000**	**42,751,000**

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2004 House Appropriations Committee Report Language (H. Rpt. 108-188)

Item

Adverse reactions to smallpox vaccine — The Committee is pleased that NIAID has focused considerable attention on research efforts aimed at reducing adverse reactions to the smallpox vaccine. The Committee understands that the risk of adverse reactions is particularly high in individuals who have or have experienced atopic dermatitis. Given the high incidence of atopic dermatitis among those with asthma and allergies, and the potential for their adverse reactions to the smallpox vaccine, the Committee is pleased that NIAID has undertaken a major initiative in this area, the atopic dermatitis and vaccinia immunization network. NIAID is encouraged to take additional steps to encourage investigator-initiated research to complement this effort. (P. 72)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is deeply committed to supporting research efforts aimed at reducing adverse reactions to the smallpox vaccine. For example, in FY 2004, NIAID will launch the Atopic Dermatitis and Vaccinia Immunization Network (ADVN) to develop and implement a research plan to reduce the risk of eczema vaccinatum (EV), a severe and potentially fatal skin disease resulting from exposure to the vaccinia virus. The ADVN will be comprised of the Clinical Studies Consortium for investigating the immune system of atopic dermatitis patients, as well as their immune responses to cutaneous viruses; the Animal Studies Consortium for developing animal models of atopic dermatitis; and the Statistical and Data Coordinating Center for data analysis, clinical coordination, regulatory activities, and patient registry development. Through this Network, NIAID will support clinical and animal studies designed to diminish or eliminate the risk of EV and other serious adverse reactions to vaccinia immunization in atopic dermatitis patients. NIAID will also continue to encourage grant applications on the pathogenesis of EV and atopic dermatitis.

The Institute continues to be actively involved in the development and testing of new vaccines, including the initiation of clinical trials to determine vaccine safety and efficacy in special populations, and is carefully examining improved alternatives to the Dryvax smallpox vaccine. Specifically, NIAID is developing modified vaccinia Ankara (MVA), which may be a viable "second generation" smallpox vaccine for people with skin conditions or immunodeficiency who are at high risk for complications from the Dryvax smallpox vaccine. NIAID's Vaccine Research Center is currently evaluating the safety of MVA administration and analyzing the immune response. As an integral part of the clinical development plan for MVA, NIAID-supported Vaccine and Treatment Evaluation Units will also conduct preliminary studies of MVA vaccine in individuals with atopic dermatitis. NIAID is also planning a phase I study of MVA in subjects with varying levels of immunosuppression due to HIV-infection.

One currently accepted treatment for adverse reactions to the smallpox vaccine is the administration of vaccinia immunoglobulin. However, this material is often in short supply because of the limited number of recently vaccinated people who could contribute plasma to its

manufacture. NIAID intramural scientists are collaborating with industry to produce an alternative – monoclonal antibodies that can neutralize the vaccinia virus. If successful, such antibodies could be prepared in large quantities, standardized and stored until needed for treatment of most of the adverse effects of smallpox vaccination.

Item

Asthma research and severe acute respiratory syndrome (SARS) — The Committee encourages NIAID to continue its strong efforts in the area of asthma research. Research in this area is closely related to research on SARS. Therapies currently used to treat SARS are commonly used to treat complications of asthma. Therefore, the Committee encourages NIAID to engage the asthma community in efforts related to SARS so that knowledge gained from studies of immune reaction to viruses in the lung among asthma patients can be applied. (p. 72)

Action to be taken

Recognizing that similarities and interrelatedness between allergic respiratory conditions, such as asthma, and infectious respiratory diseases, such as severe acute respiratory syndrome (SARS), may be important for developing effective treatments for a wide range of respiratory conditions, the National Institute of Allergy and Infectious Diseases (NIAID) maintains a broad portfolio of basic, applied and clinical research on these conditions. For example, NIAID conducts an active intramural program of asthma and inflammation research relevant to understanding the role of infectious agents, including the virus that causes SARS, in the generation of pulmonary inflammation in asthma. Current research includes laboratory studies of the immune and inflammatory reactions to various RNA viruses, including members of the Pneumovirus family.

The Institute currently supports a contract for studies on viral pathogenesis and evaluation of new viral vaccines and therapeutics against influenza, respiratory syncytial virus (RSV), SARS, and human metapneumovirus. The studies will examine, for example, the role of cytokines (molecules produced by immune system cells) in mediating response to the SARS virus. Similar immunological responses to RSV are thought to play a role in the development of reactive airway diseases such as asthma, and a better understanding of the host immune response to respiratory viruses may suggest new approaches to preventing progression from acute infection to a chronic respiratory condition, as seen in asthma. NIAID is also funding a Program Project entitled "Global Impact of Respiratory RNA Viruses on Cellular Pathways" to determine the common strategies used by respiratory RNA viruses to evade the innate immune response. The Program Project will focus on influenza and RSV, and it is anticipated that the results will extend to other respiratory RNA viruses, including the SARS virus.

NIAID supports the Asthma and Allergic Diseases Research Centers (AADRC) program, whose major goal is to define immune mechanisms involved in asthma development and progression. Since infections with RSV have been implicated in asthma susceptibility and rhinoviruses can trigger acute asthma exacerbations, several of the AADRCs have focused their research on pulmonary immune response to these viral agents. Other AADRCs have established programs in pulmonary immunobiology and cutting edge pulmonary clinical research. The infrastructure provided by the AADRC program is ideally suited to support research on the pulmonary immune response to viral infections, including SARS.

NIAID staff and several NIAID-funded SARS researchers served as external advisors at a July 2003 strategic planning meeting on SARS pulmonary research, organized by the National Heart, Lung, and Blood Institute. Topics included a discussion of the benefits and possible risks of use

of asthma treatments such as steroids to treat SARS. Such collaborations within the National Institutes of Health are an important step in integrating research on respiratory conditions such as SARS and asthma.

Future plans include encouraging grant applications on the immunopathology of SARS and studies on inflammation and airway hypersensitivity, adaptive and innate immunity, and viral immune evasion. The NIAID Tetramer Facility will synthesize reagents for the analysis of immune cells called T cells, as T cell sites that can bind to the SARS virus are identified. NIAID is also planning a randomized, double-blind, placebo-controlled trial at Muhimbili Hospital in Dar es Salaam, Tanzania, to examine the effect of zinc adjuvant therapy on the severity of pneumonia. Studies suggest that zinc and zinc-dependent enzymes may play a role in asthma and may be required for maintenance of normal structure and function of bronchial epithelial cells. If the clinical study shows that zinc is useful for treating pneumonia, it may also have applications for SARS-related pneumonia.

Item

Hemophilia — The Committee supports NIAID's efforts with voluntary organizations to ensure access for persons with hemophilia to clinical trials for improving the treatment of HIV and complications of hemophilia, including hepatitis C. The Committee urges the Institute to continue its efforts related to research on liver disease progression and response to hepatitis C treatment among HIV-infected persons with hemophilia. (p. 71)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to supporting research targeted to the HIV-infected hemophiliac population. The current scientific priorities of the HIV-infected hemophiliac population are focused on the impact of hepatitis C virus (HCV) infection. To meet this research priority, NIAID is funding a University of Cincinnati study on liver disease progression and HCV genomic variability in HIV-infected hemophiliacs. In FY 2004, NIAID will continue to fund this study of liver disease progression in HIV-infected hemophiliacs.

Item

Lupus — Lupus is a prototypic polygenic, multi-organ disease of hyperactive immune function. Therefore, by unraveling the genetic disorders that lead to lupus, much could be learned about the structure and balance of interacting forces in the body's natural defenses against infections, allergies, and cancer. The Committee encourages NIAID to enhance its research on this prototypical autoimmune disease. (p. 71)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) through its intramural and extramural programs, supports a diverse portfolio of research on autoimmune diseases, including systemic lupus erythematosus or lupus. For example, NIAID intramural scientists studying children with rare genetic forms of multi-organ autoimmunity have uncovered part of the polygenic influence that determines autoimmunity. They are using these discoveries to test DNA from patients with systemic lupus erythematosus to determine the influence of these genes on the disease process. This work and information from the human genome sequence will further our understanding of the interacting forces that determine the body's natural defenses against infections, allergies, and cancer.

The NIAID Stem Cell Transplantation for Autoimmune Diseases Consortium is developing clinical trials to assess the efficacy of adult hematopoietic stem cell transplantation to treat several severe autoimmune diseases, including lupus. Trials involving patients with lupus are expected to begin in 2004. In addition, studies of the underlying immune mechanisms of autoimmune diseases will be conducted.

NIAID, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Office of Research on Women's Health at the National Institutes of Health, supports the Autoimmunity Centers of Excellence (ACEs) to conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials of immunomodulatory therapies. In FY 2003, NIAID expanded the ACEs program to include nine distinct institutions. The ACEs are currently conducting a phase I clinical trial of anti-CD20 antibody as a potential treatment for systemic lupus erythematosus. Other single and multi-site cooperative clinical trials for new immunomodulatory interventions are in development. NIAID plans to expand the ACEs in FY 2005.

NIAID also supports the Immune Tolerance Network (ITN), an international consortium of scientists and clinicians dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases, asthma and allergic diseases, and kidney and pancreatic islet transplant rejection. The ITN, which is co-sponsored by NIDDK and the Juvenile Diabetes Research Foundation International, is developing clinical trials involving tolerance induction approaches for multiple autoimmune diseases, including lupus. Through the ITN and the ACEs, NIAID will continue to support clinical trials and assay development for promising tolerance induction and immunomodulatory strategies to treat lupus and other autoimmune diseases.

Item

Primary immune deficiency diseases — The Committee notes that more than 70 primary immune deficiency diseases have been identified to date. These diseases, which impair the body's immune system, strike most severely at children, many of whom do not survive beyond their teens or early twenties. Primary immune deficiencies afflict more than 50,000 Americans. The Committee commends NIAID for the establishment of its Primary Immunodeficiency Disease Research Consortium. As part of this new initiative, the Committee encourages the Institute to provide adequate support for primary immune deficiency research, clinical registries, and a repository for biomedical specimens. The Committee encourages NIAID to work closely with the patient community of this promising new program. (p. 71)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to supporting and conducting research to advance our understanding of the mechanisms by which primary immunodeficiency diseases occur and to develop safe and effective treatments for these diseases. NIAID-supported research on primary immunodeficiency diseases focuses on natural history, genetics, and pathogenesis and mechanisms of disease. For example, in FY 2003, NIAID renewed funding for a program project at Beth Israel Hospital in Boston, Massachusetts, to study mouse models of three primary immunodeficiencies – X-linked lymphoproliferative disease, Wiscott-Aldrich syndrome, and severe combined immune deficiency (SCID) – and for research at the University of Pennsylvania to evaluate therapies for SCID in a large animal model. NIAID continues to support clinical trials at Children's National Medical Center in Washington, DC to determine the most efficacious bone marrow transplantation regimen in patients with primary immunodeficiency diseases.

In FY 2003, NIAID and the National Institute of Child Health and Human Development (NICHD) co-sponsored and established the Primary Immunodeficiency Consortium, which will bolster primary immunodeficiency research by 1) providing resources to fund preclinical and clinical research on the underlying molecular and cellular causes of disease, to develop diagnostics and biomarkers of disease, and to evaluate innovative therapeutic strategies; 2) establishing mentoring and education programs for new investigators; and 3) expanding the patient registry and establishing a repository for biomedical specimens. Patient data and specimens will be available for use by investigators via a secure website that protects the privacy of registry participants. It is anticipated that the Consortium will support four to five pilot or small research projects in FY 2004.

The under-diagnosis of primary immunodeficiencies is another area of NIAID's focus. NIAID works in partnership with organizations, such as the Jeffrey Modell Foundation (JMF) and the Immune Deficiency Foundation (IDF), to educate the public and medical professionals about these rare diseases. For example, NIAID clinicians give lectures to the clinical community about primary immunodeficiencies and participate in scientific meetings and conferences, some of which are supported by JMF. NIAID clinicians and clinical support staff regularly communicate information about novel diagnostic tools and treatments to members of IDF and the Chronic Granulomatous Disease Association. In addition, NIAID has developed informational booklets about chronic granulomatous disease and have distributed them to patients and their families, as well as to physicians in the community. NIAID will continue to communicate important new information about primary immunodeficiency research to the community, as well as meet and collaborate with organizations with an interest in primary immunodeficiency diseases to promote physician education and public awareness.

FY 2004 Senate Appropriations Committee Report Language (S. Rpt. 108-81)

Item

Adverse reactions to smallpox vaccine — The Committee is pleased that the NIAID has focused considerable attention on research efforts aimed at reducing adverse reactions to the smallpox vaccine. The Committee understands that the risk of adverse reactions is particularly high in individuals who have or have experienced atopic dermatitis. Given the high incidence of atopic dermatitis among the growing number of Americans with asthma and allergies, the potential for adverse reactions to the smallpox vaccine is a major concern. The Committee is pleased that the NIAID has undertaken a major initiative in this area, the Atopic Dermatitis and Vaccinia Immunization Network. The Committee believes that NIAID should take additional steps to encourage investigator-initiated research to complement this effort. (Page 125)

Action to be taken

Please refer to page 47 of this document for NIAID's response to this significant item regarding adverse reactions to the smallpox vaccine.

Item

AIDS in the Soviet Union — The Committee notes that Russia and other countries of the former Soviet Union are experiencing the highest growth of HIV infections in the world today. The Committee also notes that these countries hold tremendous scientific capacity. The Committee encourages the Institute to seek opportunities to increase collaborative research between the United States and countries of the former Soviet Union in the area of HIV/AIDS research, utilizing organizations that facilitate and support scientific collaboration as appropriate, to

maximize the impact of scientific discovery. (p. 125-126)

Action to be taken

The number of HIV/AIDS cases has been growing exponentially in the Russian federation, and the National Institute of Allergy and Infectious Diseases (NIAID) is deeply committed to increasing collaborative HIV/AIDS research efforts with the countries of the former Soviet Union. Through the Comprehensive International Program of Research on AIDS (CIPRA), NIAID has awarded planning and organizational grants to the Infectious Pathologies, AIDS Control and Clinical Immunology Research Centre in Tbilisi, Georgia, to develop a HIV, hepatitis C and sexually transmitted disease research program in Georgia; and the Saint Petersburg Pavlov Medical University in St. Petersburg, Russia, to study HIV/AIDS and opportunistic infections in injection drug users.

The Biomedical Center for AIDS at Saint Petersburg University in St. Petersburg, Russia, is one of 16 international sites participating in NIAID-supported HIV Prevention Trials Network (HPTN). This site is currently conducting a 6-month prospective cohort study to characterize HIV risk behaviors and HIV incidence rates, and to establish effective standard operating procedures for future HPTN studies.

NIAID also supports several Centers for AIDS Research (CFAR) programs, including the University of North Carolina CFAR study to examine the traits of tuberculosis/HIV core transmitters among Russian injection drug users and to review Russia's HIV/tuberculosis control and prevention program. The University of Washington CFAR received NIAID funding to study the transfer of oligonucleotide ligation assay (OLA) technology to international labs and is training local health authorities in Russia to help control the spread of drug-resistant HIV. NIAID is also supporting the Johns Hopkins University and State Research Center of Virology and Biotechnology VECTOR CFAR study on the neurobehavioral model of HIV among drug users in Russia and Estonia. This study focuses on identifying cognitive profiles unique to Russians and Estonians that can be later used to foster adaptive HIV prevention interventions.

The Department of Health and Human Services (DHHS) and NIAID also support two Biotechnology Engagement Program (BTEP) grants in Russia. The BTEP works closely with the State Department's Bioindustry Initiative and the International Science and Technology Center in Moscow to patent and commercialize promising results from their collaborative efforts.

In FY 2004, NIAID will continue to support collaborative efforts by providing funding and support in the form of competitive CIPRA awards and other grants and awards to Russia and other countries of the former Soviet Union. Investigators at the University of Pennsylvania CFAR are currently assisting Russian investigators in preparing a CIPRA cooperative research project grant application.

Item

Asthma Research and Management — The Committee is very pleased with NIAID's leadership regarding asthma research and management. The Committee recognizes the role the Institute has played in the Inner City Asthma Study and the importance of this effort concerning morbidity and mortality among underserved populations, particularly children. The Committee urges NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also urges the NIAID to collaborate more aggressively with voluntary health organizations to support asthma prevention, treatment, and research activities. Additionally, recent studies suggest that a variety of viral and bacterial agents, including agents

used for immunization may play a role in the development of asthma. The Committee urges the Institute to expand research into the role that infections and vaccines may play in the development of asthma. (p. 126)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to improving the diagnosis, treatment, and prevention of asthma, particularly for inner-city children disproportionately affected by this disease. NIAID supports a diverse portfolio of research on asthma through cooperative research centers, program projects, contracts, and investigator-initiated grants. For example, in FY 2003, NIAID funded four Asthma and Allergic Diseases Research Centers (AADRCs), bringing the total number of AADRCs to thirteen. The AADRCs support basic and clinical research on the mechanisms, diagnosis, treatment and prevention of asthma and allergic diseases.

The Inner-City Asthma Study, which is co-sponsored by NIAID and the National Institute of Environmental Health Sciences, recently demonstrated that both the physician feedback intervention and environmental intervention reduced the number of unscheduled asthma visits for children. These results were presented at the 2003 annual meeting of the American Thoracic Society. NIAID translated the Inner-City Asthma Study asthma intervention into a simplified form suitable for use by community health organizations. A key element of this simplified intervention is the Child Asthma Risk Assessment Tool (CARAT), an instrument that enables caregivers to systematically analyze the asthma risks for their child and to develop an intervention strategy based on their child's asthma risk profile. NIAID is collaborating with the Centers for Diseases Control and Prevention to disseminate and implement this highly successful asthma intervention in a four-year program involving 23 community health organizations nationwide. Interim analysis of another NIAID-funded project, entitled "Early Environmental Hygiene and Pediatric Atopy," indicated that frequent use of antibiotics in infancy and early childhood is associated with the later development of asthma.

NIAID is continuing its efforts to improve asthma treatment and management. In FY 2004, the Inner-City Asthma Consortium, a network of basic scientists and clinical investigators who evaluate promising immune-based therapies to reduce asthma severity and prevent asthma onset in inner-city children, will begin a cohort project with 500 newborns at four sites. The objective of this long-range study is to understand the allergic and environmental influences on the development of asthma and the immune system. In addition in FY 2004, NIAID plans to widely distribute the CARAT and a linked repository of information related to the Inner-City Asthma Study asthma intervention through the NIAID web site. This will enable caregivers of children with asthma as well as voluntary health organizations to develop individually tailored educational, behavioral, and environmental interventions that complement traditional medication-based asthma management strategies. NIAID is also planning to establish a Pediatric Asthma Research Clinic at the National Institutes of Health Clinical Center. This clinic will provide a focal point for intramural research studies aimed at improving asthma management in children.

Advancing our understanding of the immune mechanisms that cause and exacerbate asthma, including the role of viral and bacterial infections, remains a high priority for NIAID. In FY 2004, NIAID will initiate a new program, Immune System Development and the Genesis of Asthma, which will support research on the early life changes in immune function that lead to the development of asthma and the cellular and molecular processes involved in the onset of asthma, including the effects of bacterial and viral infections and vaccines on the function of the

developing immune system. In FY 2005, NIAID plans to launch an Institute initiative, Immunobiology of Acute Asthma, which will focus on the mechanisms involved in acute exacerbations of asthma, including the cellular and molecular processes that cause some viral infections to trigger asthma attacks.

Item

Asthma research and SARS — The Committee encourages NIAID to continue its outstanding efforts in the area of asthma research. Clearly, research in this area is closely related to that undertaken by the NIAID with respect to Severe Acute Respiratory Syndrome [SARS]. The therapies currently used to treat SARS are commonly used to treat complications of asthma. The Committee urges the NIAID to engage the asthma community in efforts related to SARS so that knowledge gained from studies of immune reaction to viruses in the lung among asthma patients can be applied. (p. 126)

Action to be taken

Please refer to page 48 of this document for NIAID's response to this significant item regarding asthma research and SARS.

Item

Hemophilia —The Committee is supportive of NIAID's efforts with the National Hemophilia Foundation to ensure access for persons with hemophilia to clinical trials for improving treatment of HIV and complications of hemophilia, including hepatitis C [HCV]. The Committee urges the Institute to continue its efforts related to research on liver disease progression and response to HCV treatment among HIV/HCV co-infected persons with hemophilia. (p. 126)

Action to be taken

Please refer to page 49 of this document for NIAID's response to this significant item regarding hemophilia.

Item

Primary immune deficiency diseases — The Committee notes that more than 70 primary immune deficiency diseases have been identified to date. These diseases, which impair the body's immune system, strike most severely at children, many of whom do not survive beyond their teens or early twenties. Primary immune deficiencies afflict more than 50,000 Americans. The Committee commends NIAID for the establishment of its Primary Immunodeficiency Disease Research Consortium. As part of this new initiative, the Committee encourages the Institute to provide adequate support for primary immune deficiency research, clinical registries, and a repository for biomedical specimens. The Committee encourages NIAID to work closely with the patient community on this promising new program. The Committee remains concerned that research into biodefense concerning smallpox vaccination focus on the identification of immunodeficient patients. Undiagnosed patients are at risk of suffering serious adverse reactions to such live vaccinations. One means for NIAID to address this issue of under-diagnosis is through active participation in the Jeffrey Modell Foundation's national physician education and public awareness campaign for primary immunodeficiencies. (p. 127)

Action to be taken

Please refer to page 50 of this document for NIAID's response to this significant item regarding primary immune deficiency diseases.

Item

Radiological Exposure —The Committee urges the Institute to increase research to identify and develop effective countermeasures to acute nuclear and radiological exposure. This is in keeping with the Institute's lead role in identifying and developing countermeasures to chemical, biological, and nuclear and radiological threats. The Committee is aware of research being carried out at the Armed Forces Radiobiology Research Institute [AFRRI], including its leading radioprotectant candidate 5-androstenediol, and encourages the Institute to work with AFRRI in this critical effort. (p. 127)

Action to be taken

The development of safe and effective radiological countermeasures remains a high priority in national preparedness, and the National Institute of Allergy and Infectious Diseases (NIAID) has begun to examine and develop a research agenda for chemical, radiological and nuclear terrorism. In FY 2003, NIAID convened two expert panels in radiobiology and medical chemical defense to identify research gaps. Specifically, NIAID convened a meeting, which included scientists from NIAID, the National Cancer Institute (NCI), the Armed Forces Radiobiology Research Institute (AFRRI), the National Academy of Sciences (NAS), other government agencies, and academia, to identify priorities in the development of medical countermeasures against nuclear and radiological terrorism. NIAID convened another panel of experts to identify gaps in scientific knowledge about chemical injury and repair, and to identify priorities for the research and development of medical countermeasures.

NIAID and AFRRI have developed a partnership to initiate synergistic research endeavors in developing nuclear and radiological countermeasures, including the radioprotectant candidate 5-androstenediol. In FY 2003, NIAID funded an interagency agreement with AFRRI for the purchase of a Cobalt-60 gamma ray source to support future research efforts. In FY 2004, NIAID will negotiate another interagency agreement with AFRRI to examine the function of macrophages (host defense cells) and to measure the changes in the levels of cytokines (proteins of the immune system) in the spleen and bone marrow, following whole body irradiation and treatment with 5-androstenediol.

The FY 2004 interagency agreement with AFRRI will also include work plans to develop and validate commercial, off-the-shelf components for an automated system that will enhance throughput and standardize the current chromosome aberration-based assay for radiation dose determination. Protocols for the use of such a system to replace the current manual laboratory methods, which are both time and labor intensive, will be developed and validated. The work plans will also include identifying and validating biomarkers for radiation dose assessment, which could be used to develop a field deployable screening system that allows triage following a radiological or nuclear event. Efforts will be made to determine the effects of ionizing radiation on the pharmacokinetics, toxicity and efficacy of antimicrobial agents used to treat infections that occur after radiation exposures. Initial studies will evaluate antimicrobial agents in the Strategic National Stockpile. Finally, the work plans will involve studies examining the efficacy of substances known as isoflavones (genistein and daidzein) as radioprotectants and post exposure therapeutics.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$4,243,399,000	Indefinite	$4,364,122,000
Infectious Diseases	Section 41B	42§285b	Indefinite		Indefinite	
Infectious Diseases						
National Research Service Awards	Section 487(d)	42§288	a/	59,641,000	b/	61,385,000
Total, Budget Authority				4,303,040,000		4,425,507,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1996	$557,354,000 2/	$1,169,628,000	$549,246,000 3/	$1,169,628,000
Rescission				(676,000)
1997	584,362,000 2/	1,256,149,000	595,016,000 3/	1,257,794,000 4/
1998	634,272,000 2/	1,339,459,000	1,359,688,000	1,351,655,000
1999	703,723,000 2/5/	1,470,460,000	1,540,102,000	1,570,102,000
Rescission				(1,039,000)
2000	789,156,000 2/	1,714,705,000	1,786,718,000	1,803,063,000
Rescission				(5,025,000)
2001	935,166,000 2/	2,062,126,000	2,066,526,000	2,069,388,000
Rescission				(1,084,000)
2002	2,355,325,000	2,337,204,000	2,375,836,000	2,535,778,000
Rescission				(1,239,000)
2003	3,983,693,000	2,674,213,000	3,727,473,000	3,730,973,000
Rescission				(24,251,000)
2004	4,335,255,000	4,335,255,000	4,335,255,000	4,335,255,000
Rescission				(30,593,000)
2005	4,425,507,000			

1/ Reflects enacted supplements, rescissions, and reappropriations.
2/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $569,000.
4/ Excludes enacted administrative reductions of $575,000.
5/ Reflects an increase of $1,683,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	226	280	280
Division of Allergy, Immunology, and Transplantation	57	68	67
Division of Microbiology and Infectious Diseases	107	174	173
Division of Extramural Activities	131	172	171
Division of Acquired Immunodeficiency Syndrome	114	129	128
Division of Intramural Research	752	749	749
Total	1,387	1,572	1,568
FTEs supported by funds from Cooperative Research and Development Agreements	(7)	(7)	(7)

FISCAL YEAR	Average GM/GS Grade
2001	10.8
2002	10.9
2003	11.1
2004	11.1
2005	11.1

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Detail of Positions

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6			
ES-5			
ES-4			
ES-3			
ES-2			
ES-1			
Subtotal	0	0	0
Total - ES Salary	$0	$0	$0
GM/GS-15	66	79	79
GM/GS-14	174	207	206
GM/GS-13	166	198	197
GS-12	172	205	204
GS-11	163	194	193
GS-10	4	5	5
GS-9	84	100	99
GS-8	51	61	61
GS-7	64	76	76
GS-6	39	47	47
GS-5	13	16	16
GS-4	11	13	13
GS-3	11	13	13
GS-2	5	6	6
GS-1	3	4	4
Subtotal	1,026	1,224	1,219
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	17	17	17
Senior Grade	15	15	15
Full Grade	7	7	7
Senior Assistant Grade	1	1	1
Assistant Grade	1	1	1
Subtotal	42	42	42
Ungraded	418	418	418
Total permanent positions	1,058	1,199	1,195
Total positions, end of year	1,486	1,684	1,679
Total full-time equivalent (FTE) employment,end of year	1,387	1,572	1,568
Average ES level			
Average ES salary	$0	$0	$0
Average GM/GS grade	11.1	11.1	11.1
Average GM/GS salary	$67,103	$70,324	$72,715