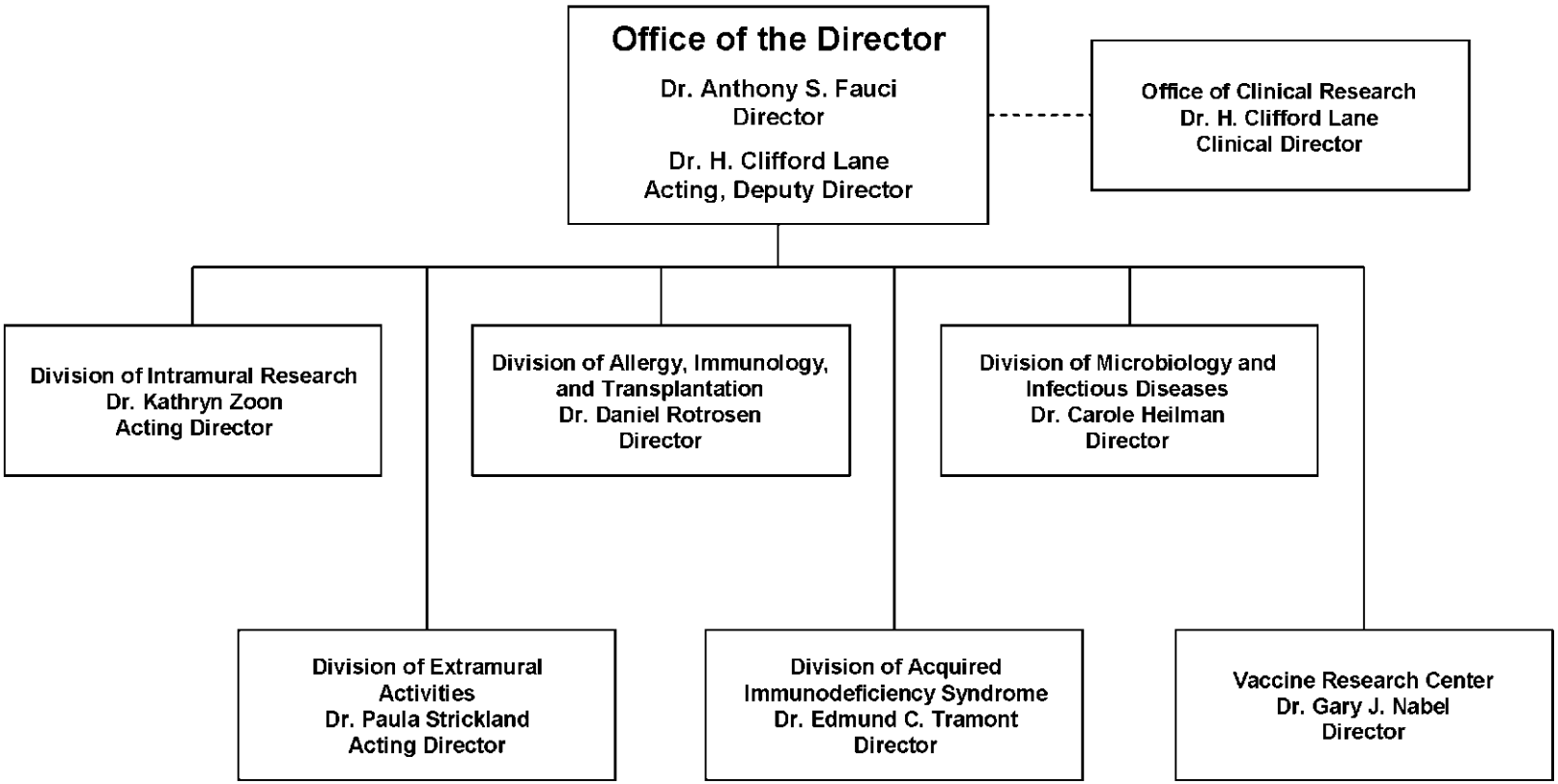
DEPARTMENT OF HEALTH AND HUMAN SERVICES

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, [$4,459,395,000] *$4,395,496,000*: Provided, That $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 [$30,000,000] *$25,000,000* shall be for extramural facilities construction grants to enhance the Nation's capability to do research on biological and other agents. *[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2006, as enacted by Public Law (109-149)]*

National Institutes of Health
National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$4,440,007,000	$4,459,395,000	$4,395,496,000
Enacted Rescissions	(37,166,000)	(44,594,000)	
Subtotal, Adjusted Appropriation	4,402,841,000	4,414,801,000	4,395,496,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(27,208,000)	(38,567,000)	
Real transfer to the Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	(99,200,000)	(99,000,000)	
Comparative transfer from OD for NIH Roadmap	27,208,000	38,567,000	
Comparable transfer from the Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	99,200,000	99,000,000	
Comparable transfer from the Public Health and Social Services Emergency Fund		18,000,000	
Comparable transfer to the OD for advanced product development		(49,500,000)	
Subtotal, adjusted budget authority	4,402,841,000	4,383,301,000	4,395,496,000
Unobligated Balance, start of year			
Revenue from Breast Cancer Stamp 2/			
Unobligated Balance, end of year			
Subtotal, adjusted budget authority	4,402,841,000	4,383,301,000	4,395,496,000
Unobligated balance lapsing			
Total obligations	4,402,841,000	4,383,301,000	4,395,496,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $3,924,000 FY 2006 - $8,000,000 FY 2007 - $8,500,000
Excludes $9,880,378 in FY 2006 and $13,954,303 in FY 2007 for royalties.

Justification

National Institute of Allergy and Infectious Diseases

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
1,549	$4,402,841,000	1,515	$4,383,301,000	1,551	$4,395,496,000	36	$12,195,000

This document provides justification for the Fiscal Year 2007 research activities of the National Institute of Allergy and Infectious Diseases (NIAID), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview Section.

INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID) is a component of the National Institutes of Health (NIH), which is an agency of the Department of Health and Human Services (DHHS). NIAID supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including illness from agents with bioterrorism potential, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis, malaria, autoimmune disorders, asthma, and allergies. Through its intramural and extramural research programs, NIAID contributes substantially to the global effort to identify and characterize infectious agents, decipher the underlying pathways by which they cause disease, and develop preventive measures and treatments for many of the world's most dangerous pathogens. NIAID research has led to advances that have improved the health of millions of people in the United States and around the world. These efforts are in support of the DHHS goal of enhancing the capacity and productivity of the Nation's health science research enterprise in order to prevent, diagnose, and treat disease and disability.

NIAID has two distinct roles in the fight against infectious and immune-mediated diseases. First, NIAID carries out a comprehensive research program on infectious and immune-meditated diseases. Second, NIAID must respond quickly to new infectious disease threats as they emerge. The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as bioterrorism; newly emerging and re-emerging infectious diseases; and the increase in asthma prevalence among children in this country. The growth of NIAID programs also has been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of microbiology, immunology, and infectious diseases. Advances in these

key fields have led to a better understanding of the human immune system and the mechanisms of infectious and immune-mediated diseases.

A brief overview of selected NIAID activities, as well as recent scientific advances and proposed new initiatives, is presented here for three separate focus areas: biodefense and emerging and re-emerging infections; HIV/AIDS, tuberculosis and malaria; and immune-mediated diseases and transplantation.

RESPONDING TO INFECTIOUS DISEASE THREATS

Some experts in the 1960s optimistically predicted that infectious diseases would cease to be important factors in human health, but infectious diseases continue to cause significant mortality and morbidity within the United States and elsewhere. Worldwide, infectious diseases account for 26 percent of all deaths, making this group of diseases the second leading cause of death. Furthermore, because infectious diseases cause approximately two thirds of deaths among children less than five years of age, the situation is even worse in terms of years of healthy life lost. Infectious diseases also seriously undermine economic development, especially in developing countries, where they are both a cause and consequence of poverty and can lead to serious political instability.

BIODEFENSE AND EMERGING AND RE-EMERGING DISEASES

The terrorist attacks on September 11, 2001, clearly exposed the vulnerability of the United States to brutal acts of terrorism. The anthrax attacks in Florida, New York, and Washington that followed only a few weeks later made it very clear that the threat of bioterrorism with pathogens or biological toxins represents a serious threat to our Nation and the world. Naturally emerging and re-emerging pathogens also pose a serious threat. The consequences of the emergence or re-emergence of an infectious disease can be staggering. For example, since HIV/AIDS first became a major public health concern in the early 1980s, it has spread relentlessly throughout the world and now threatens to surpass in total fatalities both the "Black Death" of the 14th century and the influenza pandemic of 1918-1919—two other emerging infections that each killed tens of millions of people. In the past seven years alone, West Nile and monkeypox viruses have appeared in the United States, Severe Acute Respiratory Syndrome (SARS) emerged as a new human infectious disease, and a number of human infections with avian influenza viruses have occurred. As part of the Federal government's recent efforts to prepare for a possible pandemic involving avian influenza, NIAID is supporting the development and testing of candidate avian influenza vaccines. See Story of Discovery on page 8 for details about these studies.

The threat of bioterrorism, like threats from naturally emerging and re-emerging infections, requires comprehensive and closely-coordinated efforts to identify new threats as they emerge and to develop vaccines, treatments, and diagnostic tools needed to successfully counter these new threats. In early 2002, NIAID embarked on a systematic strategic planning process that led to the development of three key documents: the *NIAID Strategic Plan for Biodefense Research*[1], *the NIAID Research Agenda for Category A Agents* and the *NIAID Research Agenda for Category B and C Agents*. Category A agents, which pose the greatest threat as potential agents of bioterror, include: anthrax, smallpox, plague, botulism, tularemia, and viral hemorrhagic

1 All NIAID biodefense research plans and agendas are on the NIAID website at http://www.niaid.nih.gov/biodefense.

fevers such as the Ebola virus. Category B priority pathogens are agents that are moderately easy to disseminate and result in moderate morbidity and low mortality; examples include food- and water-borne pathogens and viral encephalitis. Category C priority pathogens include emerging pathogens that could be adapted for use in a terrorist attack; examples include West Nile virus (WNV), multi-drug resistant tuberculosis, antibiotic resistant microbes, SARS, and influenza.

The *NIAID Strategic Plan for Biodefense Research* outlines three distinct priority areas for the biodefense research program: *basic research* on microbes and host immune defenses; targeted, milestone-driven *medical countermeasure development* to create the vaccines, therapeutics, and diagnostics that we will need in the event of a bioterror attack; and development of *infrastructure* needed to safely conduct research on dangerous pathogens. The two biodefense research agendas describe short-term, intermediate, and long-term goals for research on the wide variety of agents that could be used to conduct such an attack.

NIAID was recently given the role of coordinating and facilitating NIH research into ways to mitigate harm to civilians from chemical and radiological/nuclear weapons; other NIH institutes and centers will also contribute substantially to this effort. The *NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats* was released in June 2005, and the *NIH Strategic Plan and Research Agenda for Medical Countermeasures against Chemical Threats* is scheduled to be released in mid-2006. The strategic plans and agendas are focused on the greatest public health threats resulting from radiological or chemical terrorism.

Basic Research on Microbes and Host Immune Defenses

Advances in the field of medicine rest on a foundation of basic research into the fundamental properties and mechanisms of life. In biodefense, these basic studies include the sequencing and understanding of microbial genes (*genomics*), understanding how microbes cause disease (*pathogenesis*), and understanding how the human immune system and pathogens interact (*immunology*). NIAID-funded basic researchers have in recent years made significant progress in each of these areas.

NIAID-supported genomics researchers, for example, have determined the genetic sequence of more than 90 pathogen genomes, as well as the genome sequence of two insect vectors of disease. In many instances, multiple strains have been sequenced, providing critical information that is already assisting researchers to better understand these pathogens, such as why one strain of the same pathogen may be more virulent than another. To date, NIAID has also established the Pathogen Functional Genomics Resource Center to provide and distribute to the broader research community a wide range of genomic resources, reagents, data and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. Moreover, NIAID collaborated with numerous public and private partners to launch the Influenza Genome Sequencing Project in 2004. The goals of this project are to determine the complete genetic sequences of thousands of influenza virus strains and to rapidly provide these sequence data to the scientific community. This program will enable scientists to better understand the emergence of influenza epidemics and pandemics by observing how influenza viruses evolve as they spread through the population and by matching viral genetic characteristics with virulence, ease of transmissibility, and other clinical properties.

In pathogenesis studies, NIAID-supported researchers in collaboration with NIAID intramural scientists determined the three-dimensional structure of anthrax toxin bound tightly to a target cell surface receptor, and thus have gained a detailed snapshot of a crucial step in the pathway that allows anthrax to kill its host. Finally, studies of the human innate immune system, which is comprised of "first responder" cells and other defenses that provide a first line of defense against a wide variety of pathogens, have been moving forward rapidly. These advances suggest it may be possible to develop a relatively small set of fast-acting, broad-spectrum countermeasures that can boost innate immune responses to many pathogens or toxins. Manipulation of the innate immune system also could lead to the development of powerful vaccine additives called adjuvants that can increase vaccine potency.

Development of Medical Countermeasures Against Biological Agents

The high priority given to increasing the Nation's ability to respond effectively to infectious disease threats has led NIAID to expand the scope of its biodefense product development activities. Throughout its history, NIAID has supported research that generates new knowledge about disease, and has worked to translate these findings into vaccines, therapeutics, and diagnostics that protect public health. However, in order to move ahead more rapidly with the development of medical countermeasures while preserving excellence in basic research, NIAID has recently begun to creatively modify the traditional mechanisms of support for research and development. Working in close collaboration with industry and academia, NIAID has begun to play an expanded role in moving promising strategies for biodefense countermeasures toward advanced product development, especially in situations where market incentives are weak. The BioShield legislation of 2004 has helped in this regard by allowing NIAID to work closely with industry partners to expedite the development of critical countermeasures for biodefense and by establishing secure funding for the DHHS to purchase and stockpile new vaccines and drugs for use in an emergency. To put it another way, powerful mechanisms have been established that both "push" and "pull" science toward needed medical countermeasures—basic research provides the push and new incentives to industry for product development provide the pull.

Vaccines

Vaccines are usually the most effective method of protecting the public against infectious diseases. NIAID, in collaboration with industry and other Federal agencies, supports a robust portfolio of research on the development of new and improved vaccines against Category A, B and C agents which are suitable for populations of varying ages and health statuses. Vaccines developed to counter civilian bioterrorist attacks must be safe, easy to administer, and capable of an immediate protective and/or infection-blocking immune response. NIAID is currently supporting the development of "next generation" vaccines against smallpox and anthrax, as well as vaccines against Ebola, tularemia, and botulism.

NIAID also supports the development of vaccines against emerging and re-emerging diseases. For example, NIAID is supporting the development of multiple vaccines against influenza virus, including vaccines against the H5N1 and H9N2 influenza virus strains (see Story of Discovery on page 8). NIAID began a clinical trial in April 2005, of a WNV vaccine which was developed through research at the U.S. Centers for Disease Control and Prevention (CDC). A phase I clinical trial of a WNV vaccine developed by NIAID scientists using a different approach is

underway at Johns Hopkins School of Public Health. Several candidate vaccines against SARS have also been developed. Researchers at the NIAID Vaccine Research Center are conducting trials of one which focuses on the SARS spike protein that protrudes from the virus' outer envelope and helps it bind to the cells it infects.

Therapeutics

In the event of a bioterrorism incident or naturally occurring disease outbreak, effective therapeutics will be needed to address the immediate health needs of the public. Although antimicrobial agents for treating many viral, bacterial, and fungal infectious diseases currently exist, a more robust arsenal is needed to treat infections caused by a broad array of potential pathogens and to intervene against drug-resistant pathogen variants that may emerge. Increasing the availability of effective therapeutics, by discovery and development of novel interventions and by screening already-licensed therapeutic agents for activity against additional infectious disease threats, remains a top priority for NIAID research. Some therapeutics in development act to prevent the growth of a microbe once inside the body. For example, the antiviral drug Cidofovir prevents replication of the DNA of several viruses, including smallpox; a new oral form of the drug is now under development and testing. Other therapeutics act by neutralizing toxins or other critical virulence factors. For example, a new anthrax therapy under development includes antibodies that bind to anthrax toxin, and candidate antibody treatments for the toxin that causes botulism also are in development.

Development of Medical Countermeasures Against Radiological and Nuclear Threats

NIAID is the lead Institute at NIH for the development of medical countermeasures that could be used to treat radiation injury following a terrorist attack or accident at a nuclear facility. The *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats*, published in June 2005, outlines four distinct priority research areas: basic and translational research, methods to measure radiation doses, focused product development for medical countermeasures for radiation exposure, and infrastructure for research and product development.

NIAID recently made multiple awards to develop therapeutics to treat short-term and long-term effects of radiation exposure, as well as products to prevent or mitigate these effects and measure radiation exposure. NIAID also established interagency agreements with two other Federal research institutes, the Armed Forces Radiobiology Research Institute (AFRRI) and the NIH National Cancer Institute (NCI). Under these agreements, AFRRI will assist NIAID in the screening and evaluation of compounds that could be used to prevent, mitigate, or treat the effects of radiation exposure, as well as develop automated assays of blood cell chromosome damage that can measure a person's radiation exposure. NCI will contribute to the general understanding of the health effects of ionizing radiation, assist in the development of promising compounds to protect against radiation exposure, largely based on NCI's clinical experience in radiation therapy, and continue epidemiological studies on the medical consequences of radiation exposure.

Research Resources

Perhaps the most tangible signs of NIAID's biodefense research progress are the biocontainment research facilities now under construction, in which scientists will be able to contain and study pathogens under highly-regulated conditions that protect the researchers, the community, and the

environment. For example, through its extramural program, NIAID is supporting the construction of two National Biocontainment Laboratories—capable of safely containing the most deadly pathogens—as well as 13 Regional Biocontainment Laboratories nationwide. In addition, NIAID is building three intramural biocontainment labs, one on the NIH campus, one as part of the National Interagency Biodefense Campus at Fort Detrick in Fredrick, MD, and one at the NIAID Rocky Mountain Laboratory in Hamilton, MT. These high-level biosafety facilities promise to speed the research and development of effective therapies, vaccines, and diagnostics for diseases caused by agents of bioterror as well as naturally emerging and re-emerging diseases.

NIAID is also strengthening intellectual infrastructure for biodefense research. The Institute established a nationwide network of Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases Research. These Centers are now conducting fundamental research on infectious diseases that could be used in bioterrorism; developing diagnostics, therapeutics and vaccines needed for biodefense; providing training for future biodefense researchers; and assisting with the emergency response to natural disasters, such as hurricane Katrina. Two new RCE awards were announced on June 1, 2005, bringing the total number of RCEs nationwide to ten.

NIAID also provides numerous resources for basic research and countermeasure development to scientists nationwide. For example, NIAID-supported researchers recently developed and made available to the research community a set of screening tools to be used to evaluate compounds for activity against both bacterial and viral pathogens in cell culture and in animal models of disease. NIAID's Biodefense and Emerging Infectious Diseases Repository acquires, authenticates, stores, and distributes critical research reagents and information to qualified members of the scientific community for research and development purposes.

Science Advances – Biodefense and Emerging and Re-emerging Diseases

Potent Anthrax Neutralizing Antibody Developed

NIAID scientists and their colleagues from the Protein Biophysics Resource of NIH developed and characterized an antibody that binds to and neutralizes the anthrax toxin more tightly than any other such antibody characterized to date. The results from this study indicate that passive immunization—immunity acquired by injection of antibodies against anthrax toxin—may provide immediate protection to people exposed to anthrax; future studies will test whether the protection lasts long enough to prevent illness weeks after exposure, when inhaled *Bacillus anthracis* spores lodged in a person's lungs begin to grow.

New Rapid Diagnostic Test for Pneumonic Plague Can Be Used In Most Hospitals

Pneumonia and flu-like symptoms can be caused by common pathogens such as influenza virus, as well as by potential agents of bioterrorism such as plague. To distinguish a common illness from a possible bioterror attack, physicians need rapid diagnostic tests. In the case of plague, current tests rely on culturing organisms present in patient samples and typically take from 24 to 72 hours to generate a result. Recently, NIAID-funded scientists developed a 6-hour test to assist in the diagnosis of plague in patients with pneumonia symptoms at a hospital; most hospital laboratories, including small community hospitals, would be capable of performing this type of assay.

Flu Drug Shown Effective Against H5N1Avian Influenza Strains in an Animal Model
Experiments in mice conducted by NIAID-funded researchers have shown that an antiviral drug currently used against annual influenza can also suppress some strains of the H5N1 avian influenza virus, which has spread from birds to humans and killed dozens of people in Asia since early 2004. This study found that oseltamivir, sold commercially as Tamiflu®, dramatically boosted the survival rate of infected mice. However, the results suggested that a longer course of therapy (eight days rather than the standard five days) may be required for H5N1 than is required for seasonal flu.

Gene-based Vaccination May Provide Protective Immunity Against Diverse Influenza Viruses
Current influenza vaccines elicit antibodies effective against specific strains of the virus, but new strategies are urgently needed for protection against influenza strains that may unexpectedly emerge. DNA vaccines have been shown to protect animals against diverse virus strains, but the potency of the vaccines needs improvement. NIAID scientists recently tested in an animal model a combination of a DNA vaccine followed several weeks later with an live adenovirus engineered to contain an influenza protein called NP. The combination vaccine elicited a strong immune response and provided substantially more protection against viral challenge than DNA vaccination alone. Importantly, vaccination also protected animals against lethal challenge with highly pathogenic H5N1 avian influenza virus.

Humanized Monoclonal Antibody Shows Promise Against West Nile Virus
In humans, the natural antibody response to West Nile virus (WNV) is often successful in neutralizing the virus. Based on this principle, NIAID-supported researchers developed monoclonal antibodies against WNV. One particular antibody neutralized 10 different WNV strains in animal studies, and a single dose was able to cure mice of WNV, even after the virus had entered the brain. The researchers then developed a "humanized" version, in which the genetic material that controls the mouse antibody's targeting was cloned into a human antibody backbone. When tested in mice, the humanized antibodies retained their ability to stop West Nile virus. This successful animal study suggests that humanized antibodies may be a viable treatment for WNV and that antibody-based therapeutics may be useful in treating other infections caused by viruses that invade the brain.

Emerging Staphylococcus Strains Found to be Increasingly Deadly and Deceptive
NIAID scientists and their colleagues examined how the immune system reacts to strains of antibiotic-resistant *Staphylococcus aureus* bacteria that sicken otherwise healthy people living in a community. They found that these strains are more deadly and better at evading human immune defenses than more common *S. aureus* strains that originate in hospitals and other healthcare settings. The researchers observed that community-acquired *S. aureus* strains, which do not respond to treatment with the methicillin family of antibiotics, can efficiently evade immune defenses mounted by immune cells called neutrophils, which normally ingest and kill harmful bacterial. The scientists also identified specific *S. aureus* genes that may enable the bacteria to escape from neutrophils, which are a type of immune cell; the proteins encoded by these genes may prove to be promising drug targets.

FY 2007 New Research Initiatives – Biodefense and Emerging and Reemerging Infectious Diseases

In accordance with NIAID's Biodefense Strategic Plan and Research Agendas, as well as recent scientific meetings such as NIAID's 2004 Summit on the State of Anti-Infective Development, NIAID will launch the following research initiatives in FY 2007:

- *Development of Therapeutic Agents for Selected Bacterial Diseases:* Will advance candidate therapeutics for the Category A bacterial pathogens (anthrax, plague, tularemia) as well as those that have broad spectrum activity against an antimicrobial resistant pathogen.

- *Development of Third Generation Anthrax Vaccines:* Will conduct product development for a third generation anthrax candidate vaccine to prevent disease caused by exposure to *Bacillus anthracis* spores and other Bacilli harboring the genes that allow *B. anthracis* to cause disease.

- *NIAID Structural Genomics Centers for Infectious Diseases:* Will help to structurally characterize targeted proteins from NIAID Category A-C pathogens and organisms causing emerging or re-emerging infectious diseases. The goal is to create a collection of three-dimensional protein structures that are widely available to the broad scientific community and serve as a blueprint for structure-based drug development for infectious diseases.

- *Influenza Centers of Excellence:* Will establish multiple Centers that will expand the search for new variants of influenza viruses among animals both internationally and domestically and conduct research on influenza pathogenesis and host immune response.

- Three partnership initiatives to foster the development of partnerships between researchers from different disciplines and/or industry:

  - *Therapeutics and Diagnostics for Influenza (Partnerships for Pandemic Influenza):* Will accelerate the development of potent new antiviral agents and diagnostics for influenza.

  - *Therapeutics and Diagnostics for Category B Bacteria and Viruses:* Will support discovery/design and development of therapeutics for biodefense Category B bacteria and viruses.

  - *Therapeutics and Diagnostics for Biodefense Toxins:* Will help discover and develop novel post-exposure therapeutics and rapid and sensitive diagnostics for the botulinum neurotoxins, ricin, Staphylococcus enterotoxin B (SEB), *Clostridium perfringens*, epsilon toxin, and Shiga toxins.

Story of Discovery: Development of a Vaccine for Pandemic Influenza

In 1918 and 1919, influenza swept the globe, killing more than 500,000 people in the United States and more than 40 million people worldwide. Although no influenza pandemic of this magnitude has occurred since, public health officials are acutely aware that a future influenza pandemic could occur at any time. Recognizing the importance of preparing for such a pandemic, the National Institute of Allergy and Infectious Diseases (NIAID) maintains a robust research program designed to encourage vaccine development and enhance our understanding of influenza viruses.

Scientists and public health officials have increased their vigilance and preparedness in light of the ongoing sporadic cases of avian influenza in Asia. In 1997, a strain of influenza virus called the H5N1 avian influenza A sickened and killed both poultry and humans in Hong Kong. This virus has now spread to over 16 countries, where it has infected more than 130 people and caused at least 70 deaths. The virus does not spread easily from human to human, but public health officials are concerned that it could develop the ability to do so and, thus, spark a fast-moving global pandemic.

Innovations in Vaccine Research

Vaccines are essential tools for the control of influenza. NIAID supports many research projects to foster the development of new influenza vaccine candidates and manufacturing methods that may be simpler and more reliable than the current technology.

Influenza viruses are named for two proteins on their outer coats. One of these, called hemagglutinin (HA), allows the virus to bind to a cell and initiate infection. The other, called neuraminidase (NA), enables newly formed viruses to exit the host cell and infect other cells.

A new technique based on the principle of reverse genetics allows scientists to manipulate the genomes of influenza viruses and to transfer genes between viral strains, enabling them to rapidly generate vaccine candidates with surface proteins that precisely match a selected epidemic strain. In the conventional method of generating an influenza vaccine strain, two flu strains with the preferred features for a new vaccine are injected into a fertilized chicken egg, where their genes recombine naturally. Researchers then sift through the hundreds of possible combinations of viruses to find one that displays the desired HA and NA proteins. With reverse genetics, however, scientists use genetic engineering techniques to customize a flu vaccine strain, directly assembling genes that code for the desired features. Researchers inject the assembled genes into an animal cell, and then recover the resulting virus for use in vaccine manufacture.

One key benefit of using reverse genetics is that if portions of a targeted virus are too virulent to grow well inside eggs, the segments of the genes responsible for virulence can be removed. NIAID-supported investigators took advantage of this property when they used reverse genetics to develop a vaccine reference strain for the currently circulating H5N1 avian influenza. This vaccine reference strain was then sent to two pharmaceutical companies with contracts to manufacture pilot lots of several thousand vaccine doses. When lots of vaccine from one of the companies was delivered to NIAID in early March 2005, NIAID's Vaccine and Treatment Evaluation Units conducted a clinical trial in healthy adults. Preliminary data indicate that the vaccine is generally safe and stimulates an immune response that is predicted to be protective. Trials of this vaccine will be expanded to include testing in the elderly and children, two populations often most vulnerable to seasonal influenza. Trials with H5N1 vaccine pilot lots from the other pharmaceutical company are expected to begin in early 2006; this trial will also evaluate the use of adjuvants, a vaccine component that improves the immune response.

Innovations in Vaccine Composition

The genetic material of the influenza virus is prone to mutations, which allows it to easily evolve in ways that circumvent the human immune system. Influenza vaccines act by giving the immune system a preview of certain proteins found on the surface of the flu virus. But because the virus changes its surface proteins every season, immunity must be reestablished with a new influenza immunization every fall.

NIAID-supported scientists are working to develop vaccine candidates that, with only one immunization, may provide a broad immunity to many flu strains, including potential pandemic strains. Several scientists are using mice to test candidate vaccines made against a stable protein in the flu virus's outer coat. Other researchers are testing vaccines made from flu proteins that are less likely to be altered by mutations.

Innovations in Vaccine Production
The current system for the production of U.S.-licensed influenza vaccines uses chicken eggs to grow influenza vaccine strains. The viral particles are purified from the eggs, inactivated, and processed for distribution. Although this method is dependable, it requires at least six months—and hundreds of millions of eggs—to produce a sufficient supply of vaccine for the U.S. population. The complex logistics and long lead time required under this system make it impossible to boost the vaccine supply quickly if an emergency arises.

An alternative method shows promise, however. NIAID has awarded multiple contracts to study cell culture, an alternative means for rapidly producing large quantities of flu vaccine. Instead of injecting flu virus into eggs, cell culture uses mammalian cells grown in large culture vessels. As with the egg-based method, the virus is purified from the cells, inactivated, and processed to make doses of flu vaccine, but because additional culture vessels are relatively easy to set up, vaccine manufacturing capacity can be scaled up rapidly. In the spring of 2005, the Department of Health and Human Services (DHHS) also awarded a contract to develop and manufacture clinical investigational lots of inactivated influenza vaccines using cell culture techniques.

Other alternative methods of influenza vaccine production are also under development. For example, NIAID-supported investigators have genetically engineered baculovirus, an insect virus not related to influenza, to express genes that encode an influenza coat protein such as HA or NA. The engineered baculovirus is then grown in insect cell cultures, and the influenza protein that the virus produces is purified for use as an influenza vaccine. A recent NIAID-supported Phase II clinical trial of a vaccine of this type showed that it is well tolerated and produces an immune response. The company that produced the vaccine is conducting further clinical evaluation of this product.

Innovations in Vaccine Delivery
NIAID-supported researchers are also helping to develop novel techniques to deliver influenza vaccines. Beginning in the mid-1970s, NIAID investigators were integral to the development and clinical evaluation of a live influenza vaccine that is delivered as a nasal spray. FluMist®, a vaccine based on this research, was licensed by the FDA in the summer of 2003, and was available for the first time during the 2003-2004 flu season. Today, NIAID intramural researchers are working with colleagues from MedImmune, Inc., the manufacturer of FluMist, to produce and test a library of vaccine candidates against all known influenza strains with pandemic potential. Under a Cooperative Research and Development Agreement, NIAID and MedImmune scientists will create a substantial library of new live vaccine candidates, including at least one vaccine for each of the 16 variations of hemagglutinin. An investigational new drug (IND) application has been submitted to the FDA for one of these, against H5N1 influenza; a clinical trial of this candidateis planned for spring 2006.

Because supplies of an avian influenza vaccine will initially be limited, NIAID is supporting investigations into possible ways to stretch the available doses. NIAID-supported investigators are evaluating intradermal injection of the seasonal flu vaccine compared to the traditional intramuscular injection; intradermal delivery vaccine may yield an adequate immune response with a smaller vaccine dose. NIAID also supports research into the effectiveness of adjuvants in boosting the immune response to seasonal and pandemic influenza vaccines. An adjuvant is a substance intended to improve the immune response to the vaccine. The information obtained from studies of dose-sparing strategies will be valuable for optimizing the use of an H5N1 vaccine should it be needed.

Continued Innovations through Public-Private Partnerships
One of the fundamental elements of the NIAID pandemic influenza preparedness program is its commitment to public-private partnerships. NIAID supports government, academic, and private sector researchers who are developing new diagnostics, vaccines, and therapeutics against influenza. Through its partnerships with both U.S. and international companies, NIAID is working to develop and clinically evaluate promising new vaccines and vaccine technologies that will be crucial in the event of a pandemic outbreak.

Pandemic Preparedness
Recently, the DHHS issued the National Pandemic Influenza Preparedness Plan, which provides guidance to national, state, and local policy makers and health departments for public health preparation and response in the event of a pandemic influenza outbreak. The Plan assigns NIAID the conduct of pandemic influenza research. NIAID will continue to support scientists who study the evolution of influenza viruses and design vaccines and delivery systems to protect us from them. Through their innovations and ongoing discoveries, we will be better prepared for the next influenza pandemic.

MAJOR INTERNATIONAL SCOURGES: HIV/AIDS, TUBERCULOSIS, AND MALARIA

Infectious diseases exact a tremendous toll worldwide. The World Health Organization estimates that over 1,600 people die each hour from an infectious disease, half of whom are children under five years of age. HIV/AIDS, malaria, and tuberculosis (TB) are three of the worst killers, which together account for more than five million deaths each year[2]; in some countries in sub-Saharan Africa, these three diseases alone cause more than half of all deaths. Moreover, the prevalence of HIV/AIDS has created a large cohort of people with compromised immune systems, which in turn allows a latent TB infection to become active and spread more easily.

Because HIV/AIDS, malaria, and tuberculosis—as well as a host of other infectious diseases—occur primarily overseas, NIAID has made international research a priority. As part of its global research agenda, NIAID is pursuing a multi-faceted strategy to adapt preventive and therapeutic strategies to the needs of developing countries; to build research capacity within developing countries; to encourage global scientific partnerships; and to work with scientists in developing countries to enhance training, communications, and outreach programs. To carry out this strategy NIAID supports a number of on-going international research programs including: International Centers of Excellence in Research, International Centers for Tropical Disease Research, Tuberculosis Research Program, Comprehensive International Program of Research on AIDS, HIV Vaccine Trials Network, HIV Prevention Trials Network, and The Gambia Pneumococcal Vaccine Trial. These international research and collaborations provide the foundation for an effective global infectious diseases research program, and enhances the U.S. capacity for infectious disease surveillance and the ability to respond to newly emergent disease threats. NIAID's research goals and strategy for these diseases is outlined in The *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*[3].

HIV/AIDS

Approximately 40 million people worldwide are now infected with HIV. Sub-Saharan Africa is the hardest hit, with more than 25.3 million people infected with the virus. There are 7.4 million infected in South-East Asia 1.4 million in Eastern Europe and Central Asia, 2.1 million in Latin America and the Caribbean, 1.1 million in East Asia, 1 million in North America, 610,000 in Western and Central Europe, and 35,000 in Oceania. Although enormous scientific progress has been made in the decades since HIV was first identified as the cause of AIDS, the epidemic continues to grow, and approximately 14,000 people worldwide are newly infected with HIV every day.

HIV Vaccines

Developing a vaccine that protects against HIV infection is one of the highest priorities of the NIAID HIV/AIDS research program. The scientific challenges that must be solved to develop an effective vaccine against HIV are daunting. Perhaps the biggest obstacle is that the immune system on its own never apparently can never eradicate HIV from the body, with subsequent immunity that can ward off future infection.. Even after more than 60 million cumulative HIV infections since the beginning of the pandemic, there never has been a documented case in which

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

3 NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis, May 2001 (http://www.niaid.nih.gov/publications/globalhealth/global.pdf).

a person with established HIV infection has completely eliminated the virus. The fact that the immune system is apparently never able to defeat HIV on its own underscores the magnitude of the challenge that scientists face: a vaccine that mimics natural infection will not be good enough. Instead, a successful vaccine must do better than natural infection to induce an immune response that can prevent infection.

To help meet the challenge, NIAID established the Center for HIV/AIDS Vaccine Immunology (CHAVI) in June 2005. CHAVI's mission is to address key immunological roadblocks to HIV vaccine development and to design, develop, and test novel HIV vaccine candidates. CHAVI is a key component of the Global HIV Vaccine Enterprise, a group of independent organizations committed to accelerating the development of a safe and effective preventive vaccine for HIV/AIDS through the creation of a shared strategic scientific plan, mobilization of resources, and greater coordination among HIV vaccine researchers worldwide.

Because the vast majority of new HIV infections occur in the developing world, it is essential that HIV vaccine research address aspects of HIV natural history and pathogenesis that are unique to these regions. NIAID scientists have developed a one-two punch vaccination strategy approach, consisting of an initial (prime) vaccination followed by a later (boost) vaccination. The strategy uses a "multiclade" (i.e., multiple genetic subtype) DNA vaccine for priming vaccinations and a recombinant adenoviral vector vaccine (rAd5) for booster vaccination. The two vaccines were developed using recombinant DNA technology, and they protein variants found in HIV clades A, B, and C, which cause about 85 percent of all HIV infections around the world. Phase I clinical trials of the two vaccines indicate that they are well-tolerated and elicit cellular and humoral immune responses. A recently launched trio of trials (phase I/II) of this prime-boost strategy sponsored by the NIAID is being conducted by three international networks, the HIV Vaccine Trials Network, the International AIDS Vaccine Initiative, and the United States Military HIV Research Program to test the safety and immunogenicity of the prime-boost strategy in the Americas, South Africa, and Eastern Africa.

Therapeutics

In the United States and other developed countries, potent combinations of anti-HIV drugs called highly active antiretroviral therapy (HAART), many of which were developed with NIAID support, have dramatically reduced the numbers of AIDS deaths. Meanwhile, the toll of AIDS has accelerated elsewhere in the world, especially in poor countries where HAART regimens are too expensive for most people.

Basic research on HIV continues to provide new leads in the search for additional viral and cellular targets for antiretroviral drugs. For example, several potential drug targets have been identified in the processes used by HIV to attach itself and gain entry into the host human cell. The first of a new class of drugs, called fusion inhibitors, was recently approved by the Food and Drug Administration (FDA). In addition, at least five companies are evaluating small molecules and antibodies that inhibit the interaction between HIV and the human cell surface protein to which the virus first binds. Research on the assembly, maturation, and budding of HIV has likewise provided potential targets. Inhibitors of these and other newly identified targets are being sought by means of high-throughput screening of chemical libraries, made possible by the development of innovative assays and the application of robotics technology.

Prevention
Until we have an effective vaccine that can be widely used, control of the AIDS pandemic will likely require a combination of other strategies that can prevent HIV infection. Such approaches include topical microbicides for vaginal or rectal use, antiretroviral therapy (ART) to reduce the infectiousness of HIV-infected persons, treatment of sexually transmitted infections that are cofactors for HIV transmission, prophylactic drug treatment to prevent mother-to-child transmission, and behavioral strategies directed at individuals or communities that can reduce HIV transmission associated with sexual activity and injection drug use.

Microbicides applied as vaginal gels are a particularly promising strategy for blocking HIV transmission. A large, multi-site trial to test the safety and preliminary effectiveness of two candidate topical microbicides (PRO 2000 and BufferGel) for the prevention of HIV infection began early in 2005. This trial represents a partnership among several research institutions in Africa and the United States.

Tuberculosis
Mycobacterium tuberculosis, the bacterium that causes TB, currently infects about two billion people, or about one-third of the world's population; five to ten percent of infected people will develop active TB disease sometime in their lifetime[4]. Each year, approximately eight million new cases of active TB occur, and approximately two million people die of the disease. TB is exacerbated by co-infection with HIV/AIDS. Globally, TB is the most common cause of death in individuals infected with HIV. Moreover, antibiotics that have been indispensable in TB care for many decades are slowly losing their effectiveness as tuberculosis strains evolve resistance. Second-line therapies are often too difficult to take, not available, or too expensive to be widely implemented in countries with the highest burden of multi-drug resistant TB.

NIAID supports a large portfolio of research to develop new drugs and diagnostics, to evaluate improved therapeutic regimens, and to test vaccines to prevent TB infection. NIAID scientists are working to develop more effective drugs that would allow for shorter and less complex drug treatments, in collaboration with both the pharmaceutical industry and private-public partnerships. For example, the Global Alliance for TB Drug Development and NIAID have been working together to advance a promising new drug candidate, called PA-824, which is being tested in clinical trials. In late 2005, NIAID scientists and their colleagues identified the *Mycobacterium tuberculosis* protein targeted by PA-824, which may help scientists streamline the approach for optimizing this promising drug.

The TB vaccine that is currently available offers protection only against disseminated TB in infants and children; it provides only limited protection against TB of the lung, the most contagious form of the disease among adults and children. Recently, however, two new engineered TB vaccines developed with NIAID support entered clinical trials in the United States, the first to do so in 60 years. These studies offer an opportunity to learn more about the immune responses that protect against the TB bacterium, which are currently not completely understood. NIAID is also supporting the development of several promising TB diagnostic tests and the development of novel drug candidates.

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4 WHO Tuberculosis fact sheet, (http://www.who.int/mediacentre/factsheets/fs104/en/).

Malaria

Malaria is caused by protozoan parasites of the genus *Plasmodium* and spread by mosquitoes. Worldwide, malaria incidence is estimated to be 300 to 500 million clinical cases each year, approximately 90 percent of which occur in Africa[5]. Malaria kills approximately 1.3 million people each year, about one million of whom are African children under the age of five. The economic burden on countries with endemic malaria is high, with as much as $12 billion in lost productivity in Africa alone every year[6]. Malaria is currently resurging, largely because of the spread of drug-resistant parasite strains and insecticide-resistant mosquitoes that harbor the parasite, decay of healthcare infrastructures, unfavorable ecological changes, and difficulties in implementing and maintaining vector control programs in many developing countries.

Although there is currently no licensed vaccine against malaria, several candidates are undergoing clinical evaluation, and a much larger number of candidates are in pre-clinical development. To guide its malaria vaccine efforts, NIAID developed a research plan for malaria vaccine development[7]. One key element of this plan is to help prepare sites in regions where malaria is endemic to conduct vaccine trials, especially in sub-Saharan Africa. In addition, several sites in Africa that take a multidisciplinary approach to malaria research—combining clinical, immunologic, genetic, entomologic, and other studies—receive NIAID funding. Recently, NIAID participated in a collaboration with Walter Reed Army Institute of Research, GlaxoSmithKline Biologicals, U.S. Agency for International Development, the University of Maryland School of Medicine Center for Vaccine Development, and the University of Bamako, Mali, to conduct two phase I trials in Mali of novel candidate vaccines that target the blood-stage malaria parasites.

The complete genomes of all three organisms involved in the malaria parasite's life cycle—human beings, *Plasmodium falciparum* (the most lethal malaria-causing parasite) and *Anopheles gambiae* (a mosquito that transmits the parasite)—were recently completely sequenced, as was the genome of *P. vivax*, another parasite that causes malaria. Scientists are now mining this wealth of genomic data to gain new insights into malaria pathogenesis and to uncover new molecular targets for both drugs and vaccines. For example, genomic data have allowed scientists to discover *Plasmodium* enzymes that are very promising targets for drug intervention; NIAID and the pharmaceutical industry are currently collaborating in the development of drug candidates that can block these enzymes.

Science Advances – HIV/AIDS, Tuberculosis, and Malaria

Rapid, Massive Loss of Critical Immune Cells Occurs During Acute HIV Infection.

Scientists at the NIAID Vaccine Research Center investigated how efficiently the simian immunodeficiency virus, a model of HIV infection, depletes a crucial class of immune cells, called memory CD4+ T cells, during the acute phase of infection, and showed that the loss of these cells is extensive. The extent of the loss of these cells throughout the body—not just in mucosal tissue where the virus typically enters the host—has critical implications for vaccine development and interventional therapies.

Identifying How HIV Escapes the Body's Defenses

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5 World Malaria Report 2005 (http://rbm.who.int/wmr2005/).

6 Malaria at a Glance, World Bank Report, March 2001.

7 NIAID Research for Malaria Vaccine Development (http://www.niaid.nih.gov/dmid/malaria/malvacdv/toc.htm)

Once a person is infected, HIV mutates so rapidly that a class of immune cells called T cells cannot mount an effective response. This phenomenon, known as immune escape, appears to be a major obstacle to the development of vaccines that act by priming T cell responses. NIAID scientists examined the breadth of T cell repertoire, i.e., the number of different T cells that make up the response to the AIDS virus. These researchers showed that T cell responses that are narrow in their repertoire cannot tolerate viral mutations and allow the virus to escape rapidly. Conversely, T cell responses that have a broad repertoire are likely more able to tolerate mutations and thus can contain the virus more easily. These considerations are extremely important in helping to establish a framework on which to base rational design of HIV vaccines.

Scientists Discover Human Enzyme Crucial to HIV Replication—a Potential New Drug Target
The process of how HIV genetic material exits the cell nucleus has long puzzled scientists. Human cells cut, edit and splice RNA before it can leave the nucleus, but somehow HIV subverts that process and exports from the nucleus the long version of RNA that encodes instructions for making new viral particles. NIAID researchers found that the virus uses a human enzyme known as DDX3 to straighten its RNA before threading it through a small pore in the nucleus. The team's experiments offer the first evidence that HIV must use DDX3 to untwist its RNA molecules and move them out of the nucleus. This host cellular enzyme represents a potential new target for developing improved HIV drugs. Although it would take many years to develop, an inhibitor for DDX3 might effectively block HIV replication.

Combination Microbicides Protect Monkeys Against HIV-Like Virus
Experiments in female monkeys have shown that combinations of topical microbicides can protect against infection with the HIV-like virus SHIV. The researchers tested three microbicide gels both alone and in combination; each of the three was designed to block SHIV from entering specific cells in the vaginal area and thereby prevent the virus from invading the monkey's body. This research suggests that combination microbicides might provide a safe, effective and practical way to prevent HIV transmission to women.

A Tuberculosis Drug Resistance Protein Mimics DNA
NIAID-supported investigators have identified a new *M. tuberculosis* protein that, by a previously unknown mechanism, helps the microbe resist damage from fluoroquinolones, a class of antibiotics that binds bacterial DNA and interferes with DNA replication. The newly discovered protein, called MfpA, binds to bacterial DNA and protects it from the drug's action. MfpA is the first antibiotic-resistance protein discovered that binds to a drug's target, rather than working directly on the drug. The investigators speculate that MfpA may have a role in the basic regulation of bacterial growth. Besides elucidating details of the mechanism of action of MfpA, future work could involve re-engineering the protein to kill, rather than protect, TB bacteria.

Vaccine Based on Genetically Modified Malaria Parasites Successfully Immunizes Mice
NIAID-supported scientists recently identified a gene (*uis3*) that is highly expressed in the early, liver-associated stages of rodent malaria. In addition, they identified a similar gene in *Plasmodium falciparum*, the parasite responsible for the most lethal of the human malarias. They found that when they genetically disabled (knocked-out) this gene, not only did the host immune system easily eliminate the "knockout" parasite, but the immune response mounted by these mice later protected them against infection with fully-functioning malaria parasites. These

experiments demonstrate that a malaria vaccine based on genetically disabled whole-organism malaria parasites might elicit protective immunity in humans.

Scientists Discover How Hemoglobin C Protects Against Malaria
In some regions of West Africa, up to one-fourth of the children carry hemoglobin C, a variant of hemoglobin that can reduce the risk of severe and fatal malaria by as much as 80 percent. But how hemoglobin C conferred this protection has been a puzzle. NIAID scientists and a team of international collaborators found that hemoglobin C reduces expression of a key parasite protein called PfEMP-1. Normally, malaria parasites place PfEMP-1 on the surfaces of infected red blood cells, where it causes these cells to adhere to the lining of blood vessels in the brain and other critical tissues. Severe disease often results from the inflammation and circulatory obstruction that results. Hemoglobin C, however, alters the membranes of red blood cells so that malaria parasites have trouble placing PfEMP-1 at the surface. The infected red cells are thus less able to adhere and the severity of disease is reduced. Other hemoglobin variants, such as the sickle-cell mutation, may protect against malaria by a similar mechanism. These findings suggest that interventions affecting the display of PfEMP-1 may reduce the impact of malaria.

IMMUNE-MEDIATED DISEASES AND TRANSPLANTATION

The immune system defends the body against potentially harmful organisms such as, bacteria, viruses, and fungi and plays an important role in blocking cancer and other diseases. In some instances, however, the immune system attacks the body's own cells and tissues to cause an autoimmune disorder, or overreacts to an otherwise innocuous substance, causing allergies or asthma. The immune system also attacks transplanted organs, tissues, and cells, causing transplant rejection. In the setting of severe infection, the host immune and inflammatory response can also damage organs and tissues, causing circulatory collapse, kidney and liver failure, and neurologic impairment. When there are intrinsic defects in the cells of the immune system, often due to an inherited genetic defect, immunodeficiency disorders result.

NIAID conducts research into how the immune system and pathogens interact, as well as research relevant to all immune-mediated diseases, including primary immunodeficiency diseases, autoimmune diseases, asthma and allergic diseases, and rejection of transplanted organs, tissues, and cells. This research will expand our understanding of the basic mechanisms of the immune system and identify new avenues to treat and prevent immune mediated disorders.

Immune Tolerance

The immune system protects against infection by identifying microorganisms and viruses as "foreign" and initiating immune responses to rid the body of these agents. Likewise, a healthy immune system recognizes cells and tissues in transplanted organs as "foreign" or distinct from the other cells and tissues of the transplant recipient and initiates immune responses, that if not blunted with immunosuppressive drugs, will lead to rejection of the transplant. Understanding the mechanisms by which the immune system learns to attack "foreign" organisms, cells and tissues, and to "tolerate" the cells and tissues it recognizes as "self" may someday enable researchers selectively to block or prevent harmful immune responses such as transplant rejection while leaving protective immunity intact. This field of research, known as "Immune Tolerance" is particularly relevant to autoimmune diseases, allergies and asthma, and transplantation of organs, tissues, and cells.

Research on the induction, maintenance, and loss of immune tolerance is a high priority for NIAID. A major component of this effort is the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia that is dedicated to the clinical evaluation of novel, tolerance-inducing therapies in kidney transplantation, islet transplantation, autoimmune diseases, asthma and allergic diseases, and the immune-mediated rejection of transplanted organs, tissues, and cells. The ITN was established in FY 1999. It is co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International. The ITN supports more than two dozen studies and has established state-of-the art core laboratory facilities to conduct integrated mechanistic studies and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. NIAID also supports several other research programs on immune tolerance. These include the Innovative Grants in Immune Tolerance research program and the Non-Human Primate Transplantation Tolerance Cooperative Study Group.

Asthma and Allergic Diseases

Asthma and allergic diseases are the sixth leading cause of chronic illness in the United States[8]. Since 1991, NIAID has supported research to develop effective behavioral, educational, and environmental interventions to reduce the severity of asthma among inner-city children. The Inner-City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity is a network of basic and clinical investigators evaluating immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. Previous research supported through NIAID's Inner-City Asthma Study (co-funded by the National Institute of Environmental Health Sciences) showed that an individualized intervention to reduce allergens in a child's environment reduces health service use. Recent findings show that treatment costs would be substantially lower if interventions were implemented in a community setting, and that they would be as cost-effective as many drug interventions. In FY 2005, the NIAID established the Food Allergy Research Consortium to conduct basic, clinical, and epidemiological studies, and develop educational programs aimed at parents, children, and healthcare providers. NIAID also supports 13 Asthma and Allergic Diseases Research Centers, which conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases.

Autoimmune Diseases

More than 80 chronic and often debilitating diseases are due at least in part to inappropriate immune-mediated attack on the body's own organs, tissues, and cells. Many of these autoimmune diseases are rare, but collectively they affect between 15 and 24 million people in the United States[9]. Few treatments are available, and there are no cures. People living with an autoimmune disease often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. And, because most of these diseases disproportionately afflict women, and are among the leading causes of death for young and middle-aged women, they impose a heavy burden on patients' families and on society.

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8 NIAID Allergy Statistics (http://www.niaid.nih.gov/factsheets/allergystat.htm).

9 U.S. Department of Health and Human Services, National Institutes of Health, *Autoimmune Diseases Coordinating Committee, Autoimmune Disease Research Plan*. Bethesda, MD, 2002.

NIAID directs the Autoimmune Diseases Coordinating Committee (ADCC), which was established by NIH in 1998, and is comprised of representatives from NIH Institutes and Centers involved in autoimmune disease research, other Federal agencies, and a number of private organizations concerned with autoimmune diseases. In 2002, the ADCC prepared and presented to Congress the *Autoimmune Diseases Research Plan*[10], which sets forth an ambitious and comprehensive research agenda to generate more accurate epidemiologic profiles of autoimmune diseases; develop a greater understanding of the fundamental biologic principles underlying disease onset and progression; devise improved diagnostic tools; create more effective interventions; and produce public and professional education and training programs. In March 2005, the ADCC published a report detailing the progress that has been made since the release of the Research Plan[11].

NIAID supports a broad range of basic and clinical research programs on autoimmunity, including several multicenter research programs. For example, NIAID, in collaboration with the NIH Office of Research on Women's Health, has established nine Autoimmunity Centers of Excellence that conduct collaborative basic and clinical research on autoimmune disease. Another program, the Autoimmune Diseases Prevention Centers, conducts research that seeks new ways to prevent autoimmune diseases.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases are caused by inherited genetic defects, in contrast to secondary or acquired immune deficiency diseases, which are usually caused by infections or exposure to toxic chemicals or radiation. More than 100 different forms of primary immunodeficiency diseases exist. Most of these are rare, but taken together they affect nearly half a million Americans[12].

NIAID-supported research in primary immunodeficiency diseases strives to understand the causes of these diseases and is also expanding the understanding of the genetic basis of these disorders. This research has improved diagnostic capabilities and may lead to new protective and therapeutic treatments. The Primary Immunodeficiency Diseases Consortium, co-sponsored by the National Institute of Child Health and Human Development, helps to prioritize and coordinate research directions and develop new resources for the study of these disorders. The Consortium solicits, reviews, and makes awards for pilot or small research projects; maintains a primary immunodeficiency diseases registry that provides data to the research community about the clinical characteristics and prevalence of these diseases; and develops a repository of specimens from subjects with primary immunodeficiency diseases.

Transplantation

Over the past 30 years, the development of immunosuppressive agents and the refinement of surgical techniques has made transplantation of organs, tissues, and cells the preferred treatment

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10 ibid.

11 U.S. Department of Health and Human Services, National Institutes of Health. *Autoimmune Diseases Coordinating Committee, Progress in Autoimmune Diseases Research*. Bethesda. MD, 2005. (http://www3.niaid.nih.gov/about/organization/dait/PDF/ADCC_Final.pdf).

12 CDC, *Applying Public Health Strategies to Primary Immune Deficiency Diseases*. 2004, (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5301a1.htm).

for end-stage organ disease. In 2004, 27,000 patients received solid organ transplants and over 17,000 received hematopoietic cell transplantation in the United States alone[13]. Although the one-year survival rate has markedly improved over the past 15 years, further improvement in long-term graft, patient survival, and quality of life for transplant recipients is needed.

In 2005, NIAID convened an expert panel to develop a five-year action plan for NIH transplantation research, and will present the findings to Congress in 2006. NIAID continues to support transplantation research on the immune system mechanisms that govern acceptance or rejection of grafts, therapies to improve graft survival and function, and the use of animal tissues and organs for human transplantation. NIAID-supported programs include the Immune Tolerance Network, Cooperative Clinical Trials in Pediatric Transplantation and the Genomics of Transplantation Cooperative Research programs, as well as several trans-NIH programs, such as the Clinical Islet Transplantation Consortium, Clinical Trials in Organ Transplantation, and Clinical Outcomes of Live Organ Donors.

Science Advances – Immune-Mediated Diseases

Insulin Implicated as the Initiating Autoantigen in the Development of Autoimmune Diabetes

Two NIAID-funded studies have found that antibodies against insulin initiate the immune system attack on the pancreas in type 1 diabetes. One of these studies also demonstrated that in a mouse model of type 1 diabetes, modifying the gene for insulin prevents the onset of the disease. Together, these results suggest that insulin drives the immune reaction against the pancreas in type 1 diabetes and that immune interventions that block autoimmune reactions against insulin might prevent the development of diabetes.

A Common Infection May Set Stage for Lupus

Immune responses to infectious organisms contribute to the development of certain autoimmune diseases in some people. When this occurs, the protective immune responses against the infection cross-react with normal cells and tissues, triggering an autoimmune disease. NIAID-funded researchers recently tested the hypothesis that Epstein Barr virus (EBV) can trigger systemic lupus erythematosus (SLE). Researchers had previously shown that the antigen that initiates the autoimmune response in SLE is the RNA-binding protein Ro. The researchers hypothesized that antibody cross-reactivity with Ro and an EBV protein could be an early event in the disease. To test this hypothesis, the scientists immunized rabbits with small proteins matching the cross-reacting portions of Ro or a small fragment of the EBV protein EBNA-1. Strikingly, both groups of rabbits developed lupus-like symptoms. These findings suggest that the antibody response to EBV, a common human virus, triggers the onset of SLE through molecular mimicry. This knowledge provides a clear target for early and specific intervention, which could block the disease process before symptoms appear.

Novel Therapy for Severe Allergic Diseases Developed

NIAID-funded scientists have developed a potentially safer approach to allergen immunotherapy. Using a model of cat allergy, they have genetically engineered a potentially therapeutic molecule, called GFD, which is a fusion protein comprised of a fragment of human immunoglobulin G (IgG) and the major cat allergen (Fel d1). GFD binds to two molecules on the surface of mast cells and basophils, the major effector cells of human allergic diseases. The Fel

13 The Organ Procurement and Transplantation Network, (http://www.optn.org/).

d1 end of GFD binds to allergic (immunoglobulin E, IgE) antibodies to the cat allergen, while the IgG fragment binds to a receptor for IgG. The simultaneous engagement of the IgG receptor produces an inhibitory signal strong enough to block the activating signals that arise from the binding of allergen to IgE. In allergic mice, GFD effectively blocked allergic reactions and prevented severe systemic reactions. These results suggest that with further development, molecules like GFD might be effective measures to prevent severe allergies if proven safe and effective in additional preclinical studies and clinical studies in humans.

Defective Gene Linked to Two Inherited Immune Deficiencies
Defects in a single gene can result in two immune system disorders: immunoglobulin A (IgA) deficiency and common variable immunodeficiency (CVID). IgA deficiency affects 1 in 600 people in the Western world but is asymptomatic in many cases; CVID is less common but more severe. Both conditions can result in increased susceptibility to pneumonia and to recurring infections of the ear, sinus and gastrointestinal tract. Individuals with CVID also have an increased risk of developing some tumors. NIAID-funded researchers showed that one mutation in a protein that controls the types of antibodies made by the immune system is a cause of both IgA deficiency and CVID diseases. This research identifies a genetic cause for some cases of these primary immunodeficiency diseases and will allow genetic testing and early diagnosis.

FY 2007 New Research Initiative –Allergy, Immunology, and Transplantation

- *Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases:* will facilitate identification of novel allergens using innovative purification methods, and generate a set of regulatory peptides that researchers can use to investigate the immune mechanisms that cause allergies.

NIH ROADMAP
The NIAID mission is to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. Fulfillment of this mission increasingly relies on complex partnerships and multidisciplinary studies. NIAID's biodefense and emerging diseases research portfolio, for example, covers the spectrum from basic research in microbial physiology and basic immunology through advanced product development of vaccines, therapeutics and diagnostics. Because the NIH Roadmap emphasizes improvement of infrastructure and available resources, challenges conventional paradigms of the nature and composition of biomedical research teams, and provides leadership for embracing innovative research, the NIAID will derive benefits from its successful implementation.

The Short Programs for Interdisciplinary Research Training, Training for a New Interdisciplinary Research Workforce and Second Phase of the NIH Roadmap Exploratory Centers for Interdisciplinary Research initiatives support the development of multi-disciplinary teams representing a broad spectrum of experience and provide models for establishing highly collaborative research groups. These types of research teams are needed to implement many biodefense initiatives including, for example, the Partnerships for Biodefense, for extramural grantees, as well as the Trans-NIH/FDA Intramural Biodefense Program.

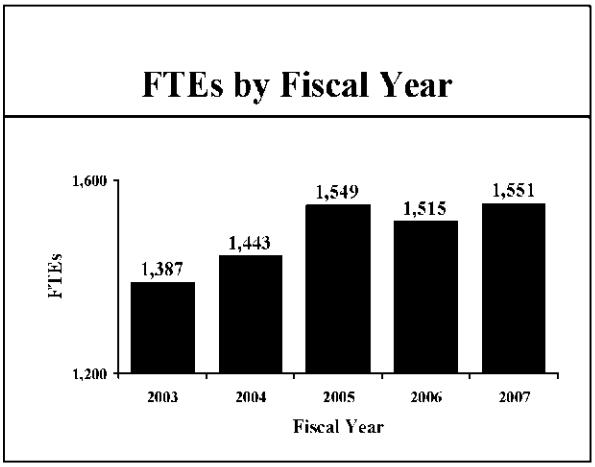
The planning and implementation grants for Institutional Clinical and Translational Science Awards will support NIAID's efforts to improve clinical research, particularly in the context of

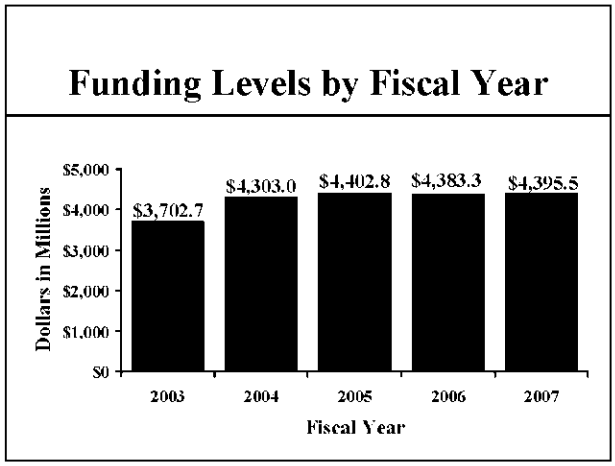
advanced product development. These activities are intended to increase the speed with which new knowledge moves from the laboratory bench to the patient bedside, and thereby speed the delivery of critical products for public health, such as new flu vaccines and therapeutics.

Budget Policy

The Fiscal Year 2007 budget request for the NIAID is $4,395,946,000, an increase of $12,195,000 and 0.3 percent over the FY 2006 Appropriation. Included in the FY 2007 request, is NIAID's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. 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 as the result of several administrative restructurings in recent years, FTE data is non-comparable.





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 pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $363,268 in FY 2007. However, the NIAID average cost comparison for competing RPGs is skewed by the large average cost of HIV/AIDS Clinical Trials Networks included in the FY2006 competing RPG pool. There is no increase in the average cost of FY2007 competing RPGs after adjusting the FY2006 amount for the large Clinical Trials Networks. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIAID has committed to a programmatic increase for an award, such increases will be provided.

NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIAID, $540,000 will be used to support 6 awards for the new K/R "Bridges to Independence" program. NIAID will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $2,174,000 to support this project.

NIAID will support the President's Initiative on Pandemic Influenza with $35 million, which is included in FY2007 request. The NIAID Pandemic Influenza Preparedness Program supports research in the following major areas: 1) Expand clinical infrastructure to support selection, research, and clinical evaluation of flu countermeasures, 2) Support testing, evaluation, and drug production in several South East Asian countries where bird flu is endemic, and 3) Expand human/animal interface studies to better understand how the avian flu virus is transferred.

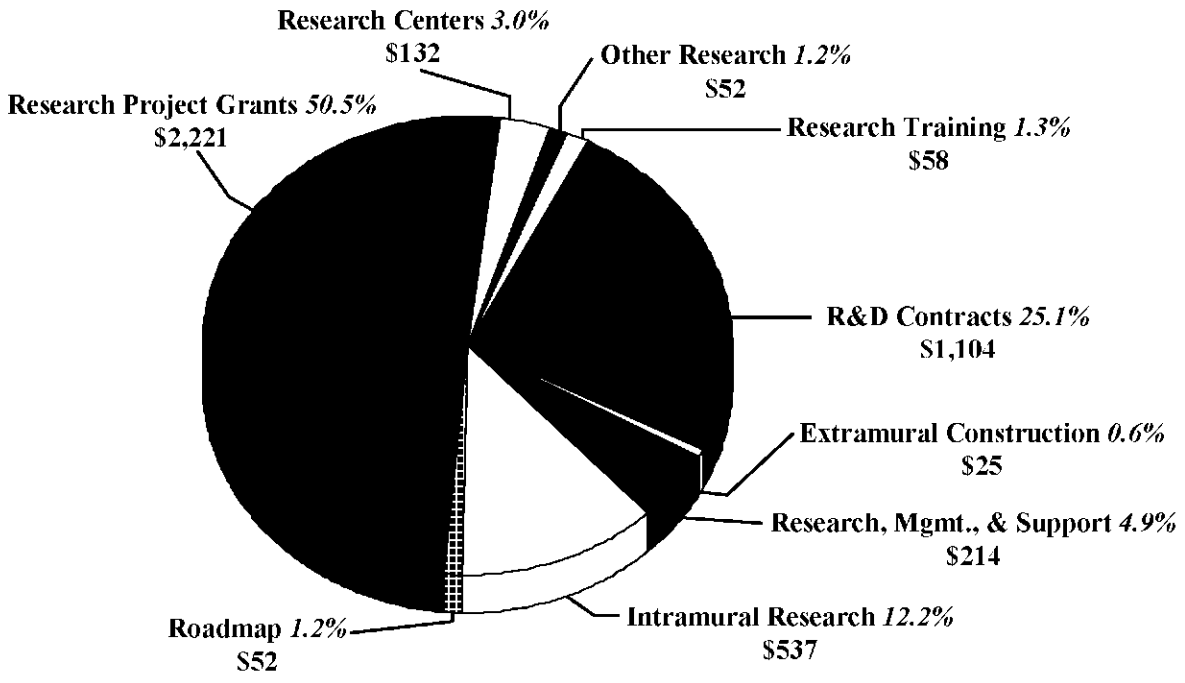
In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 34 research centers, 397 other research grants, including 326 career awards, and 338 R&D contracts. Intramural Research decreases by 0.3 percent. Research Management and Support increases by 1.5 percent.

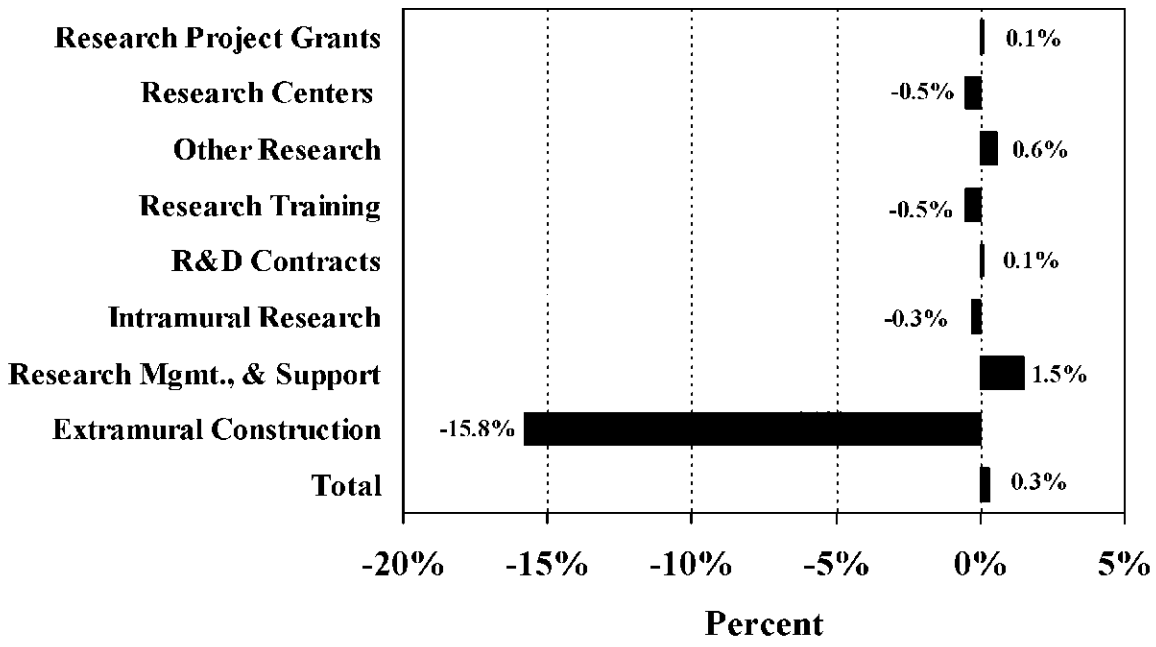
The mechanism distribution by dollars and percent change are displayed below:

FY 2007 Budget Mechanism

Dollars in Millions



FY 2007 Estimate
Percent Change from FY 2006 by Mechanism



NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,977	$1,356,810,000	3,067	$1,450,975,000	3,123	$1,685,169,000
Administrative supplements	(151)	252,151,000	(68)	16,813,000	(36)	14,005,000
Competing:						
Renewal	(296)	114,067,000	(345)	108,061,000	(338)	106,878,000
New	(867)	376,401,000	(793)	546,440,000	(821)	314,150,000
Supplements	(1)	73,000	(0)	0	(0)	0
Subtotal, competing	1,164	490,541,000	1,138	654,501,000	1,159	421,028,000
Subtotal, RPGs	4,141	2,099,502,000	4,205	2,122,289,000	4,282	2,120,202,000
SBIR/STTR	222	101,940,000	220	97,689,000	224	101,210,000
Subtotal, RPGs	4,363	2,201,442,000	4,425	2,219,978,000	4,506	2,221,412,000
Research Centers:						
Specialized/comprehensive	34	132,722,000	34	131,262,000	34	130,607,000
Clinical research		0	0	0	0	0
Biotechnology		0	0	0	0	0
Comparative medicine		300,000	0	297,000	0	295,000
Research Centers in Minority Institutions	0	1,626,000	0	1,608,000	0	1,600,000
Subtotal, Centers	34	134,648,000	34	133,167,000	34	132,502,000
Other Research:						
Research careers	326	39,903,000	322	39,464,000	326	39,808,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	1,052,000	0	1,040,000	0	1,035,000
Other	72	17,405,000	71	10,785,000	71	10,729,000
Subtotal, Other Research	398	58,360,000	393	51,289,000	397	51,572,000
Total Research Grants	4,795	2,394,450,000	4,852	2,404,434,000	4,937	2,405,486,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	187	7,913,000	181	7,826,000	180	7,789,000
Institutional awards	1,078	51,136,000	1,059	50,574,000	1,054	50,321,000
Total, Training	1,265	59,049,000	1,240	58,400,000	1,234	58,110,000
Research & development contracts	312	1,038,053,000	331	1,103,134,000	338	1,104,365,000
(SBIR/STTR)	(0)	(213,000)	(0)	(213,000)	(0)	(213,000)
	FTEs		FTEs		FTEs	
Intramural research	780	527,708,000	780	538,336,000	782	536,792,000
Research management and support	769	207,573,000	735	210,730,000	769	213,891,000
Cancer prevention & control	0	0	0	0	0	0
Construction		148,800,000	0	29,700,000	0	25,000,000
Buildings and Facilities		0	0	0	0	0
NIH Roadmap for Medical Research	0	27,208,000	0	38,567,000	0	51,852,000
Total, N	1,549	4,402,841,000	1,515	4,383,301,000	1,551	4,395,496,000
(Clinical Trials)		(651,934,000)		(651,751,000)		(654,603,000)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity

(dollars in thousands)

ACTIVITY	FY 2005 Actual FTEs	FY 2005 Actual Amount	FY 2006 Appropriation FTEs	FY 2006 Appropriation Amount	FY 2007 Estimate FTEs	FY 2007 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Extramural research		$3,640,352		$3,595,668		$3,592,961		($2,707)
Subtotal, Extramural research		3,640,352		3,595,668		3,592,961		(2,707)
Intramural research	780	527,708	780	538,336	782	536,792	2	(1,544)
Res. management & support	769	207,573	735	210,730	769	213,891	34	3,161
NIH Roadmap for Medical Research	0	27,208	0	38,567	0	51,852	0	13,285
Total	1,549	4,402,841	1,515	4,383,301	1,551	4,395,496	36	12,195

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Summary of Changes

FY 2006 Estimate				$4,383,301,000
FY 2007 Estimated Budget Authority				4,395,496,000
Net change				12,195,000
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$110,326,000		$1,578,000
b. Annualization of January 2006 pay increase		110,326,000		867,000
c. January 2007 pay increase		110,326,000		1,861,000
d. One less day of pay		110,326,000		0
e. Payment for centrally furnished services		74,847,000		1,123,000
f. Increased cost of laboratory supplies, materials, and other expenses		353,163,000		8,197,000
Subtotal				13,626,000
2. Research Management and Support:				
a. Within grade increase		80,082,000		1,358,000
b. Annualization of January 2006 pay increase		80,082,000		631,000
c. January 2007 pay increase		80,082,000		1,354,000
d. One less day of pay		80,082,000		0
e. Payment for centrally furnished services		28,179,000		423,000
f. Increased cost of laboratory supplies, materials, and other expenses		102,496,000		2,460,000
Subtotal				6,226,000
Subtotal, Built-in				19,852,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Summary of Changes--continued

CHANGES	FY 2006 Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,067	$1,467,788,000	56	$231,386,000
b. Competing	1,138	654,501,000	21	(233,473,000)
c. SBIR/STTR	220	97,689,000	4	3,521,000
Total	4,425	2,219,978,000	81	1,434,000
2. Research centers	34	133,167,000	0	(665,000)
3. Other research	393	51,289,000	4	283,000
4. Research training	1,240	58,400,000	(6)	(290,000)
5. Research and development contracts	331	1,103,134,000	10	1,231,000
Subtotal, extramural				1,993,000
	FTEs		FTEs	
6. Intramural research	780	538,336,000	2	(15,170,000)
7. Research management and support	735	210,730,000	34	(3,065,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		29,700,000		(4,700,000)
10. Buildings and Facilities		0		0
11. NIH Roadmap for Medical Research	0	38,567,000	0	13,285,000
Subtotal, program		4,383,301,000		(7,657,000)
Total changes	1,515		36	12,195,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	1,515	1,551	36
Full-time equivalent of overtime & holiday hours	6	6	0
Average ES salary	$0	$0	$0
Average GM/GS grade	11.6	11.6	0.0
Average GM/GS salary	$78,523	$80,251	$1,728
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$84,539	$86,399	$1,860
Average salary of ungraded positions	110,627	113,061	2,434

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$81,563,000	$87,220,000	$5,657,000
11.3 Other than Full-Time Permanent	45,789,000	48,437,000	2,648,000
11.5 Other Personnel Compensation	4,536,000	4,813,000	277,000
11.7 Military Personnel	3,410,000	3,628,000	218,000
11.8 Special Personnel Services Payments	16,904,000	17,634,000	730,000
Total, Personnel Compensation	152,202,000	161,732,000	9,530,000
12.0 Personnel Benefits	35,764,000	38,040,000	2,276,000
12.2 Military Personnel Benefits	2,416,000	2,585,000	169,000
13.0 Benefits for Former Personnel	26,000	28,000	2,000
Subtotal, Pay Costs	**190,408,000**	**202,385,000**	**11,977,000**
21.0 Travel & Transportation of Persons	7,927,000	7,887,000	(40,000)
22.0 Transportation of Things	862,000	854,000	(8,000)
23.1 Rental Payments to GSA	33,000	33,000	0
23.2 Rental Payments to Others	8,124,000	8,245,000	121,000
23.3 Communications, Utilities & Miscellaneous Charges	5,833,000	5,920,000	87,000
24.0 Printing & Reproduction	979,000	969,000	(10,000)
25.1 Consulting Services	3,274,000	3,179,000	(95,000)
25.2 Other Services	153,925,000	152,391,000	(1,534,000)
25.3 Purchase of Goods & Services from Government Accounts	503,114,000	504,660,000	1,546,000
25.4 Operation & Maintenance of Facilities	29,930,000	30,080,000	150,000
25.5 Research & Development Contracts	871,507,000	866,773,000	(4,734,000)
25.6 Medical Care	2,124,000	2,124,000	0
25.7 Operation & Maintenance of Equipment	10,770,000	10,661,000	(109,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**1,574,644,000**	**1,569,868,000**	**(4,776,000)**
26.0 Supplies & Materials	37,104,000	35,604,000	(1,500,000)
31.0 Equipment	26,253,000	23,253,000	(3,000,000)
32.0 Land and Structures	8,000	8,000	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	2,492,534,000	2,488,593,000	(3,941,000)
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	25,000	25,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**4,154,326,000**	**4,141,259,000**	**(13,067,000)**
NIH Roadmap for Medical Research	**38,567,000**	**51,852,000**	**13,285,000**
Total Budget Authority by Object	**4,383,301,000**	**4,395,496,000**	**12,195,000**

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$81,563,000	$87,220,000	$5,657,000
Other Than Full-Time Permanent (11.3)	45,789,000	48,437,000	2,648,000
Other Personnel Compensation (11.5)	4,536,000	4,813,000	277,000
Military Personnel (11.7)	3,410,000	3,628,000	218,000
Special Personnel Services Payments (11.8)	16,904,000	17,634,000	730,000
Total Personnel Compensation (11.9)	**152,202,000**	**161,732,000**	**9,530,000**
Civilian Personnel Benefits (12.1)	35,764,000	38,040,000	2,276,000
Military Personnel Benefits (12.2)	2,416,000	2,585,000	
Benefits to Former Personnel (13.0)	26,000	28,000	2,000
Subtotal, Pay Costs	**190,408,000**	**202,385,000**	**11,977,000**
Travel (21.0)	7,927,000	7,887,000	(40,000)
Transportation of Things (22.0)	862,000	854,000	(8,000)
Rental Payments to Others (23.2)	8,124,000	8,245,000	121,000
Communications, Utilities and Miscellaneous Charges (23.3)	5,833,000	5,920,000	87,000
Printing and Reproduction (24.0)	979,000	969,000	(10,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	3,274,000	3,179,000	(95,000)
Other Services (25.2)	153,925,000	152,391,000	(1,534,000)
Purchases from Govt. Accounts (25.3)	212,069,000	210,861,000	(1,208,000)
Operation & Maintenance of Facilities (25.4)	29,930,000	30,080,000	150,000
Operation & Maintenance of Equipment (25.7)	10,770,000	10,661,000	(109,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**409,968,000**	**407,172,000**	**(2,796,000)**
Supplies and Materials (26.0)	37,034,000	35,534,000	(1,500,000)
Subtotal, Non-Pay Costs	470,727,000	466,581,000	(4,146,000)
Total, Administrative Costs	**661,135,000**	**668,966,000**	**7,831,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

SIGNIFICANT ITEMS IN HOUSE AND SENATE
APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Asthma - The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee encourages NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also encourages 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 may play a role in the development of asthma. The Committee recommends that the Institute consider expanding research into the role that infections and vaccines may play in the development of asthma. (p. 76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues to support research aimed at reducing the impact of asthma on the lives of children and adults through prevention, treatment, and management. For example, the Institute supports thirteen Asthma and Allergic Diseases Research Centers that conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma.

To improve our asthma management efforts, especially related to children, the NIAID intramural program opened a pediatric allergy clinic at the National Institutes of Health (NIH) Clinical Center. In collaboration with NIAID intramural laboratories, the new clinic will conduct translational research and clinical trials of novel therapies. The NIAID also supports the Inner-City Asthma Consortium (ICAC) to evaluate the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. Current ICAC studies include investigations of markers for asthma severity and the immunologic causes of recurrent wheezing. The ICAC is also planning a study of the safety and efficacy of Xolair (omalizumab) in inner-city children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroid.

The NIAID collaborates with community health organizations to promote asthma prevention, treatment and research. Using results of the National Cooperative Inner-City Asthma Study (NCICAS), which was conducted in collaboration with the Centers for Disease Control and Prevention, NIAID-supported researchers developed the Child

Asthma Risk Assessment Tool, or CARAT. With this tool, caregivers can develop an asthma intervention strategy tailored to their child's asthma risk profile.
In addition, the Institute supports Demonstration and Education research projects that target asthma in medically underserved, predominately inner-city Hispanic and African American populations. These projects include school-based studies to identify children with asthma and implement strategies to reduce asthma severity.

The NIAID participated with other NIH Institutes, federal agencies, and non-federal investigators in the Asthma Workgroup of the National Children's Study (NCS), which was one of the groups involved in the initial planning of the NCS. This study, which is led by the National Institute of Child Health and Human Development, is evaluating the effects of environmental exposures on the natural history of diseases in a cohort of 100,000 individuals followed from before birth to age 25.

The Institute continues to support research on the mechanisms of asthma, including the cellular and molecular processes that cause some viral respiratory infections to trigger asthma attacks. The NIAID and the National Heart, Lung, and Blood Institute co-sponsor the Immune Development and the Genesis of Asthma program aimed at understanding early life changes in immune function that lead to the development of asthma, and the Asthma Exacerbations: Biology and Disease Progression program to elucidate the underlying pathobiology and mechanisms of asthma exacerbations.

The NIAID will continue to support research to understand the development and exacerbation of asthma, as well as strategies for asthma prevention and management.

Item

Bioterrorism - Respiratory pathogens that cause life-threatening pneumonia are commonly proposed agents of bioterrorism. The following are associated with acute pneumonia/lung injury: anthrax, smallpox, plague, and tularemia. The Committee encourages further research on the mechanisms of pneumonia by these respiratory pathogens and the development of new therapeutic interventions to reduce injury and death. (p. 78)

Action taken or to be taken

The National Institutes of Allergy and Infectious Diseases (NIAID) is the lead Institute within the National Institutes of Health for research related to potential agents of bioterrorism. The NIAID's biodefense research agenda includes both short- and long-term research targeted at the design, development, evaluation, and approval of diagnostics, therapies, and vaccines that would be needed to control a bioterrorist-caused infectious disease outbreak.

Basic research on anthrax, smallpox, plague, and tularemia will increase knowledge of how these infections could lead to respiratory infections such as pneumonia. The NIAID

supports a broad portfolio of such research. For example, NIAID-supported researchers have discovered critical host-defense mechanisms against tularemia in a mouse model.

The NIAID's Biodefense and Emerging Infectious Diseases Research Opportunities initiative encourages the submission of investigator-initiated research grant applications to expedite research leading to the diagnosis, prevention and treatment of diseases caused by potential bioterrorism agents. Recent awards through this initiative include support for research on pulmonary responses to Category A pathogens, which include anthrax, smallpox, plague, and tularemia and are considered by the Centers for Disease Control and Prevention (CDC) to be the worst bioterror threats; research on the basis of anthrax-induced vascular damage, and evaluation of lung-targeted antivirals against the poxviruses.

In addition, the NIAID has developed several initiatives that are targeted to the development of therapeutics for biodefense. The initiative, Therapeutics for CDC Category A Agents: Bioshield Accelerated Product Development, supports research projects focused on the design and preclinical development of therapeutics for CDC Category A agents, including anthrax, smallpox, plague, and tularemia.

Another initiative—Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense and SARS—supports discovery, design and development of vaccines, therapeutics, adjuvants, and diagnostics for biodefense. Through the program, *In vitro* and Animal Models for Emerging Infectious Diseases and Biodefense, the Institute is screening existing antimicrobials, which are already approved by the Food and Drug Administration, for activity against pneumonic plague and inhalational anthrax.

In 2005, the NIAID completed a national network of ten Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs) to support research focused on countering threats from bioterror agents and emerging infectious diseases. Each Center is comprised of a consortium of universities and complementary research institutions serving a specific geographical region. The research being conducted within the RCEs spans a broad range of biodefense and emerging infectious disease topics.

The capability to detect and counter a bioterrorist attack depends to a substantial degree on the state of the relevant medical science, and basic research provides the essential underpinning. The NIAID will continue to support research targeted at the design, development, evaluation, and approval of the specific public health tools — including diagnostics, therapies and vaccines — that would be needed in the case of a bioterrorist-caused outbreak.

Item

Coinfection research – The Committee is concerned that there is growing evidence of liver toxicity resulting from HIV treatment protocols such as highly active antiretroviral therapy (HAART) in those with chronic viral hepatitis and those with decompensated

liver disease awaiting liver transplantation. There also appears to be an emerging problem of liver cancer in co-infected patients. The Committee encourages NIAID to initiate research initiatives in both of these areas. (p. 77)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) maintains its commitment to the study of AIDS-associated opportunistic infections and co-infections, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), that affect people with impaired immune systems who are unable to fight off pathogens. Despite the fact that potent highly active antiretroviral therapy (HAART) has prolonged survival and reduced the incidence of opportunistic infections and co-infections in HIV-infected individuals, complications and side-effects associated with HAART have become an increasing concern for the medical management of HIV-infected individuals. In particular, individuals co-infected with HIV and hepatitis are experiencing therapy-related liver complications now being addressed by the scientific research community.

In response to the scientific research needs in this aspect, NIAID-supported researchers at Johns Hopkins University (JHU) are studying liver disease and HIV-HBV co-infection in patients on HAART through the Liver and Pancreatic Disease in HIV Infection research initiative. This initiative is intended to stimulate research on the pathogenesis and therapeutics of the liver and pancreatic diseases associated with HBV and HCV co-infections that occur in patients with HIV infection, including complications associated with treatment of HIV infection. The NIAID is also conducting the Solid Organ Transplant in HIV study on the outcome of kidney and liver transplants in HIV-positive subjects who achieved viral suppression with HAART, many of whom are co-infected with HCV or HBV.

In addition, NIAID's Adult AIDS Clinical Trials Group (AACTG) formed the Hepatitis Research Agenda Committee (HepRAC) which aims to develop clinical protocols to answer scientific questions in the areas of treatment and management, viral dynamics, immunology, and genomics of HIV/HCV and HIV/HBV co-infections as well as HCV and HBV monoinfections. The emphasis of the HepRAC is on the development of strategies for the optimal timing and treatment of each viral infection and for the treatment of drug resistance and salvage therapy. The HepRAC will also be looking at non-hepatitis steatosis, hepatoxicity, fatty liver disease, and drug interactions particularly with antiretrovirals or other drugs used in the treatment of AIDS. Currently, the AACTG is conducting a study to evaluate the safety and efficacy of interferon-based therapies such as PEG-interferon in persons co-infected with HIV and HCV.

During fiscal year 2006, the NIAID will continue to support research at JHU through the Liver and Pancreatic Disease in HIV Infection research initiative as well as the Solid Organ Transplant in HIV study. In addition, the AACTG will continue to conduct clinical trials to study treatment strategies, such as PEG-interferon, and treatment-associated complications in HIV and hepatitis co-infected individuals.

Item

Detection of disease and bioterror agents- The Committee recognizes the potential threat to national security posed by terror attacks involving biological, chemical, nuclear, and radiological weapons. One of the challenges facing public health officials responding to such an attack is the limited ability to diagnose exposure to these agents in the non-sick-appearing and early illness individuals. The Committee recognizes that disease outbreaks—such as SARS in Asia and Canada, avian influenza in East Asia, and Ebola and Marburg virus in Africa—demonstrate that the speed of diagnosis and implementation of public health measures can mean the difference between an isolated outbreak and a global pandemic. The Committee commends NIAID for its initiatives that provide comprehensive genomic, bioinformatics, functional genomics, and immune cell proteomic research resources to the scientific community conducting basic and applied research on infectious agents and the immune system. The Committee encourages NIAID to maintain its support of these programs, which provide a critical resource for the scientific community that could lead to the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics and immunotherapeutics. (p.79)

Action taken or to be taken

Deliberate exposure of the civilian population of the United States to Bacillus anthracis spores in 2001 revealed our vulnerability to a possible bioterrorist attack and our needs for diagnostic tests, interventions, and treatments after exposure to biological, chemical, nuclear, and radiological weapons. To meet these needs, the National Institute of Allergy and Infectious Diseases (NIAID) supports a number of initiatives that will lead to a deeper understanding of the many cellular components of the human immune system, how they interact with pathogens, and what changes they undergo in these interactions.

For example, the NIAID supports the Systems Approach to Innate Immunity-Inflammation-Sepsis collaborative project. This multi-year, cooperative agreement supports a multidisciplinary team of researchers who are employing a systems biology approach to create a comprehensive picture of innate immunity, an essential first line of defense against bacterial, viral, and fungal diseases. The goals of this program include the identification of the proteins expressed and the biochemical pathways triggered by encounters between innate immune system cells and infectious agents. The Institute also supports the Biodefense Proteomics Collaboratory program to identify and quantify the differential expression of key proteins in immune system cells in response to potential bioterror pathogens.

NIAID's efforts in this area also include the development of searchable electronic databases. For example, the Institute supports the Bioinformatics Integration Support Contract (BISC) to develop a platform for the organization, analysis, and integration of basic and clinical immunological data, including proteomic data. The goal of the BISC is to further our understanding of the basis of innate and adaptive immunity by providing advanced computer support for scientific data handling and disseminating best practices in scientific data analysis. The BISC will provide the means for scientists to easily

access, generate, analyze, and exchange complex high-quality data sets. The NIAID Biodefense Proteomics Research Programs initiative will facilitate the identification of new targets for potential future diagnostics, therapeutics, and vaccines. A component of this program includes the development of a web-based platform for public distribution of all data and reagents generated in the research centers of the program.

In fiscal year 2007, the NIAID will establish the program, Systems Approach to Immunity and Inflammation. The primary objective of the program is to develop an encyclopedia of innate and adaptive immune responses to microbial infection, with a focus on NIAID Category A-C priority pathogens. Research teams will be required to meld genomics, proteomics, immunology, and bioinformatics into a systems biology approach.

Item

Food allergies – The Committee is concerned about the high prevalence of food allergies, among children in particular, with up to eight percent affected. The Committee recognizes that 30,000 individuals require emergency room treatment for food allergies each year, that 100 to 200 individuals die each year from allergic reactions to food, and that there is currently no cure for food allergies. The Committee is encouraged by the March 2005 release of a report in *The Journal of Allergy & Clinical Immunology* containing guidelines for the definition of anaphylaxis, and hopes that these guidelines will improve the diagnosis, treatment, and understanding of food allergy and anaphylaxis. NIAID is encouraged to invest in research into the causes of food allergies and its potential treatments. (p.77)

Action taken or to be taken

Allergic reactions in children and adults from food allergy vary in severity and can result in the need for emergency room medical care, or in more serious cases can result in death. Reducing the burden of food allergy through targeted research in allergy and immunology through research consortia and networks continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID).

In response to the recommendations made by a panel of experts in 2003, in fiscal year (FY) 2005, the NIAID established the Food Allergy Research Consortium to conduct basic, clinical and epidemiological studies, and to develop educational programs aimed at parents, children, and healthcare providers to develop new approaches to treat and prevent food allergy. An additional grant will fund a statistical center to support the Consortium. The Consortium's first project is a clinical study to evaluate a potential therapy for peanut allergy.

Another example of research directed toward improving the diagnosis, treatment, and understanding of food allergy and anaphylaxis is a project of the NIAID-supported Immune Tolerance Network (ITN). The ITN is developing a clinical trial to determine whether feeding a peanut-containing snack to young children at risk of developing peanut

allergy will prevent development of this allergy. Study participants will include children between four and ten months of age who have atopic dermatitis and/or are allergic to eggs.

Future plans for food allergy research include the National Institutes of Health Food Allergy Expert Panel, which will be convened in March 2006. The panel will review current basic and clinical research efforts related to food allergies and make recommendations to the Secretary of Health and Human Services for enhancing and coordinating research activities related to food allergies. The panel's recommendations are expected in the fall of 2006.

In FY 2007, the Institute plans to establish the Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases program to identify novel allergens and reagents to facilitate the development of therapeutic strategies to treat and prevent allergies. In addition, the NIAID plans to re-compete the ITN to continue support of clinical trials of tolerance induction to prevent or treat asthma and allergic diseases, including food allergy.

Item

Genetic tools for infectious disease research - The Committee believes that, with regard to both biodefense and public health, the development by NIAID of multi-pathogen identification arrays that can be used to identify infectious agents through epidemiological outbreak surveillance is critically important. The use of whole genome expression, all exon transcription analysis and whole genome SNP analysis studies to identify and understand host biomarkers that may identify the type, severity and likely response to therapeutics of infectious agents holds great promise. The Committee encourages NIAID to pursue these lines of inquiry. (p. 79)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) has made a significant investment in large-scale sequencing projects that continue to generate DNA sequence information. The NIAID has launched initiatives, including the Microbial Sequencing Centers, the Pathogen Functional Genomics Research Center, and the Proteomics Centers, to provide comprehensive genomic and proteomic resources to the scientific research community. The Institute has completed genome sequencing of over 50 pathogens and continues to support pathogen sequencing projects. In addition, microbial genomics is being used together with the human genome sequence to better understand the host immune response and an individual's genetic susceptibility to pathogens. These sequencing efforts are expected to accelerate the pace of research on infectious diseases, to enhance the understanding of the pathogen's biology and its ability to cause disease, and to lead to new strategies for prevention and treatment.

The NIAID supports a number of projects to develop multi-pathogen identification microarrays. Examples include a DNA microarray diagnostic chip that will detect 18

bacterial pathogens and 25 viruses and will also be able to detect genetic changes in these organisms; polymerase chain reaction (PCR) assays that distinguish up to 60 different species-specific DNA sequences in a single assay well; and an integrated microarray detection platform combined with sample preparation technology on a CD-type format.

Microbial genomics is being used together with the human genome sequence to better understand the host immune response and an individual's genetic susceptibility to pathogens. The NIAID supports an initiative, Population Genetics Analysis Program: Immunity to Vaccines/Infections, to characterize polymorphisms in human immune response genes (including the expression patterns of innate and adaptive immune response genes) after natural infections with, or after vaccination against, pathogens and to examine the functional significance of these responses. These studies will provide a better understanding of immune responses to infection and vaccination, which may lead to identification of novel immunotherapeutic targets for vaccines and drugs to prevent and treat infections.

The NIAID is also supporting host biomarker studies, including utilization of mass spectrometry and aptamer technology to develop protein arrays for host response diagnostic signatures and the construction of a complete gene expression profile of both monkeypox virus and its host to better understand the ability of monkeypox viruses to alter the host response mechanism.

To support NIAID intramural investigators, NIAID's Microarray Research Facility (MRF) provides expertise and resources for all phases of microarray-based research projects. In addition to mouse and human arrays, MRF has produced custom microarrays to address a variety of research needs. These include microarrays for *Mycobacterium tuberculosis* (which causes tuberculosis), *Plasmodium falciparum* (which causes malaria), and *Cryptococcus neoformans* (which causes fungal infections).

The NIAID will continue to promote research projects that take advantage of the availability of microbial and human genome sequence data and that examine the functional analyses of gene and protein expression in microbial genomes.

Item

Hemophilia – The Committee encourages NIAID to continue its efforts with voluntary organizations in developing and advancing research initiatives for addressing hepatitis C (HCV) within the bleeding disorders community. The Committee understands that HCV continues to have a devastating impact on this community, with nearly half of all persons with hemophilia having contracted HCV from blood clotting factor products. (p. 76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to the support of research targeted to the HIV-infected hemophiliac population. The current scientific needs of the HIV-infected hemophiliac population are focused on the impact of

hepatitis C virus (HCV) infection. To meet the research needs in this area, the Institute is supporting a University of Cincinnati study of liver disease progression and HCV genomic variability in HIV-infected hemophiliacs. The NIAID will continue to support this study in fiscal year 2006, through a no-cost extension.

In addition, NIAID extramural program staff recently met with the leadership of the National Hemophilia Foundation to discuss ways in which the Foundation's constituency, in which there is a prevalence of HCV infection, might participate in NIAID-supported clinical trials.

Item

Hepatitis C virus (HCV) vaccine development--The Committee is encouraged to learn that a small hepatitis C vaccine human trial has been successfully completed. The Committee urges NIAID to begin to implement the results of the recent workshop that was held to discuss and evaluate efforts toward development of HCV vaccines with the goal of spurring their development and testing. The Committee also encourages NIAID to proceed with phase two of the human clinical trial as soon as it is scientifically practicable. Additionally, NIAID is urged to foster the development of an in vitro culture system for HCV as well as new animal models for basic research. The Committee continues to be concerned about the prevalence of hepatitis and urges NIAID to work with public health organizations to promote liver wellness, education, and prevention of hepatitis. (p.77)

Action to be taken

Please refer to page 58 of this document for NIAID's response regarding hepatitis and hepatitis C vaccine development.

Item

Inflammatory Bowel Disease –The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) entitled "Challenges to Inflammatory Bowel Disease." This report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to enhance its support of research focused on the immunology of IBD, as well as the interaction of genetics and environmental factors in the development of the disease. (p. 76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues its long standing commitment to research directed toward understanding and reducing the burden of inflammatory bowel disease (IBD). Since 1998, when the NIAID sponsored a workshop on Crohn's disease, the Institute has initiated cross-disciplinary research including studies that investigate the genetic and environmental factors that contribute to

IBD. The NIAID plans to sponsor a follow-on workshop to the 1998 workshop titled, "Discoveries in Microbial Etiology of Crohn's Disease."

The NIAID intramural program has expanded laboratory research on the immunology of IBD and is conducting clinical trials of promising new therapies. The intramural program in translational medicine for IBD has developed a number of clinical trials of novel drugs at the National Institutes of Health (NIH) Clinical Center. For example, NIAID scientists completed a Phase II trial of a novel immune-based therapy for Crohn's disease. In this trial, researchers evaluated the safety and efficacy of monoclonal anti-IL-12 antibody, which has shown promise as an effective treatment of active disease. This finding paves the way for a larger Phase III trial.

NIAID's extramural initiatives and programs such as the Autoimmunity Centers of Excellence, the Immune Tolerance Network and the Autoimmune Disease Prevention Centers provide opportunities for trans-NIH collaboration on IBD. For example, the NIAID participates in the Digestive Diseases Interagency Coordinating Committee led by the National Institute of Diabetes and Digestive and Kidney Diseases. The Committee facilitates research on digestive diseases including the immunology, genetics and role of the environment in IBD pathogenesis.

One of the recently-established units of the NIAID Food and Waterborne Diseases Integrated Research Network has recently begun to explore the feasibility of developing an animal model of human Crohn's disease. Such an animal model could prove valuable in research on the associations between *Mycobacterium avium* subspecies *paratuberculosis* and Crohn's disease. In addition, the NIAID supports research projects under the fiscal year 2002 initiative, Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection, co-sponsored by the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the NIH Office of Research on Women's Health. The purpose of research grants supported through this initiative is to identify and validate the role of pathogens in chronic diseases, including Crohn's disease.

The NIAID is committed to finding the cause of Crohn's disease and will continue ongoing research efforts towards this goal. In addition, the Institute will continue to pursue research to examine the role of regulatory cells in inducing and maintaining remission in IBD and to collect in depth clinical and immunologic data and specimens for genetic data to enable the identification of hereditary, environmental, and other variables that will predict or modify IBD treatment success.

Item

Islet transplantation – The Committee commends NIDDK and NIAID for the establishment of the Clinical Islet Transplantation Consortium and the islet transplantation clinical trial that will include Medicare-eligible individuals whose transplant and related costs will be covered by Medicare. The Committee urges

cooperation between NIDDK and NIAID and members of the Consortium to ensure the timely launch of these clinical trials. (p. 77-78)

Action taken or to be taken

The Clinical Islet Transplantation Consortium (CITC), which is co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), was established in 2004, to design and perform studies of islet transplantation in patients with type 1 diabetes. Islet cell transplantation has shown to be a highly effective treatment for managing type 1 diabetes.

The CITC has developed and implemented a program of single- and multi-center clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. The studies will focus on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes. Some studies will focus on improving combined islet and kidney transplants in patients with type 1 diabetes and kidney failure, a common complication of diabetes.

The Consortium will conduct clinical trials at seventeen sites, including five international centers. Currently, the CITC has five Phase II and two Phase III clinical trials in development to: (1) provide data to support licensure of an islet product for treatment of type 1 diabetes in patients with normal kidney function; (2) provide data to support licensure of an islet product for treatment of Medicare beneficiaries who have type 1 diabetes and have undergone a kidney transplant; and (3) investigate innovative approaches to improve upon current outcomes in islet transplantation. The NIAID anticipates that the CITC clinical studies will begin enrolling study participants in fiscal year 2006.

Item

Meningococcal disease/Serogroup B immunization research – Although meningococcal disease is vaccine-preventable in most cases, approximately 30 percent of the deaths and disabilities from this bacterial infection are attributed to serogroup B which is not vaccine-preventable. The Committee encourages NIAID to increase research efforts to develop an effective, low-cost vaccine against serogroup B that will help protect infants and adolescents in the near term.

Action taken or to be taken

A major goal of the National Institute of Allergy and Infectious Diseases (NIAID) Respiratory Diseases Program is to stimulate and support research that may lead to more effective and accepted prophylactic and therapeutic approaches for the prevention and

control of respiratory infections, including the development of a vaccine against serogroup B meningococcus.

In October 2004, the NIAID and the National Vaccine Program Office of the Department of Health and Human Services co-sponsored a workshop entitled "Carbohydrate Moieties as Vaccine Candidates." This workshop brought together research scientists, clinicians, and representatives from industry to identify research needs and scientific gaps in an effort to promote vaccine development for meningococcal disease. The workshop examined the mechanisms involved in the generation of an appropriate host immune response to selected antigens, highlighted recent advances, and discussed how this information could be used to advance the development of effective vaccines. This workshop included a discussion of the obstacles involved with the development of a vaccine against serogroup B meningococcus; the results of the workshop were published in *Clinical Infectious Disease* in September 2005.

The Institute continues to support pre-clinical and clinical studies to control selected human respiratory pathogens through its Respiratory Pathogen Research Units (RPRUs). Respiratory pathogens studied at the RPRUs include meningococci, pneumococci, group A streptococcus, pseudomonas, *Chlamydia pneumoniae* and non-typable *Haemophilus influenzae*.

The NIAID will continue to pursue research in support of the development and licensure of vaccines and therapeutic agents for respiratory pathogens. Among the Institute's goals are to further the understanding of the etiology and long-term health impact of acute respiratory infections and to stimulate basic research that may provide additional information on the pathogenesis, immunity, and functional components of respiratory pathogens.

Item

Nasal aerosol and spray vaccine delivery systems - The prevention of infectious diseases through the effective use of vaccines has saved mankind untold suffering and death. Recent developments exploring new routes of immunization such as delivery of measles vaccine via the aerosol route and nasal spray give great hope for achieving this goal, generating significant savings, and resulting in fewer side effects than immunization by injection. The Committee encourages NIAID to support research in developing and testing these new approaches and translating this research into public benefits. The Committee recommends that NIAID build upon the testing already completed in older children by investigating this delivery method in younger children. The Committee believes that NIAID and other institutes should collaborate with physicians and researchers working with these newer and possibly superior methods of vaccine delivery in the hopes of developing safer, more effective, and less expensive vaccine delivery modes. (p. 78)

Action taken or to be taken

Research leading to new and improved vaccines, including innovative vaccine delivery systems, is a high priority for the National Institute of Allergy and Infectious Diseases (NIAID). For example, the NIAID intramural research program has a long history of development of vaccines against childhood diseases and of research in the nasal delivery of vaccines. The work of NIAID scientists was critical to the development of FluMist, the influenza vaccine made for nasal delivery. NIAID researchers are currently developing several candidate vaccines that are specifically designed for nasal delivery. A live, attenuated, intranasal vaccine candidate against respiratory syncytial virus (RSV) was recently evaluated in infants and shown to be well-tolerated, immunogenic, and protective against a second vaccine dose. NIAID scientists also are developing human metapneumovirus vaccine candidates for nasal administration. The goal is to develop an intranasal pediatric vaccine that can be given together with aerosol vaccines being developed against RSV and the three parainfluenza viruses.

NIAID-supported researchers recently evaluated the immunogenicity of an aerosol measles vaccine in 9-month-old infants. The results suggest that a low-dose measles vaccine given by aerosol is safe and effective in inducing measles-specific T-cell immunity in most children. The research team is now developing a study protocol to evaluate, in infants, the safety and efficacy of the measles-rubella (MR) vaccine delivered by aerosol.

In addition, NIAID scientists have developed vaccines for two strains of avian influenza, H9N2 and H5N1, designed to be administered directly to the respiratory tract. Such live, attenuated vaccines generally induce broadly cross-reactive protection, which may be a useful feature in the event of a pandemic in which a vaccine generated from the actual pandemic strain is not available. A clinical trial of the H9N2 vaccine is currently underway.

The NIAID is also supporting the development of several other non-injection vaccines, including an inactivated intranasal influenza vaccine; an intranasal SARS vaccine; an adenovirus-vectored nasal anthrax vaccine; and a skin patch anthrax vaccine. In addition, the NIAID is supporting development of a nasal vaccine delivery vehicle that is suitable for delivering a number of different types of bacterial and viral antigens.

The NIAID will continue to conduct and support research on novel methods for the production and delivery of vaccines through both intramural research and grant and contract mechanisms.

Item

Nontuberculous Mycobacteria (NTM) - Mycobacteria are environmental organisms found in both water and soil that can cause significant respiratory damage. The Committee is aware of the increasing incidence of nontuberculous mycobacteria [NTM] pulmonary infections in women, particularly involving rapidly growing mycobacteria, an inherently resistant subspecies. The Committee encourages NIAID to advance diagnostic and treatment protocols for patients suffering from NTM diseases. Further, the Committee recommends additional focus on research leading to a better understanding of NTM by establishment of an inter-institute coordinating committee to facilitate cooperation between NIAID, NHLBI, and other institutes. (p. 78-79)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues to pursue research towards the improvement of the detection, diagnosis and treatment of patients suffering from nontuberculous mycobacteria (NTM) infection.

In 2005, NIAID researchers initiated the creation of the Nontuberculous Mycobacteria Consortium (NTMC) in an effort to advance diagnostic and treatment protocols for NTM and to promote collaborative efforts to increase the understanding of NTM. The Consortium is a nationwide network of research centers that are working to identify and understand the epidemiology, pathophysiology, diagnosis, therapy, and outcomes of NTM. The network includes seven centers with research or clinical programs focused on NTM and two centers with programs in NTM related to their focal area of cystic fibrosis. These two centers link to a network of other clinical cystic fibrosis centers in North Carolina and New York. The NTMC is currently developing a clinical protocol to compare the efficacy and toxicity of several treatment regimens in patients with pulmonary mycobacterium avium complex infection.

NIAID researchers have long standing collaborations across the National Institutes of Health (NIH) with colleagues who are also investigating NTM. A four-year, NIAID collaboration with the National Heart, Lung, and Blood Institute's (NHLBI) Pulmonary Branch is examining cystic fibrosis genetics in patients with NTM infections. This collaboration has resulted in a major study on the frequency of certain gene mutations in patients with pulmonary NTM disease. This and other collaborations will be enhanced by the addition of a pulmonologist at the NIAID who will serve as a liaison to NHLBI and the NIH Critical Care Medicine Department on pulmonary diseases.

Studies planned for the future include a multi-year study to identify and characterize the clinical, microbiologic, immunological, and genetic aspects of NTM infection; a protocol to study the use of immune adjuvants in patients with NTM infection, and a study of the use of mefloquine for treating pulmonary *Mycobacteria abscessus* infection.

Item

Primary immunodeficiency diseases – NIAID is the lead agency for research into this class of diseases that is known to afflict about 500,000 Americans and may affect an equal amount that have not yet been diagnosed. To address the complex research needs of this group of about 140 separate diseases, the NIAID has created a research consortium comprised of the leading experts in primary immunodeficiency diseases. The Committee requests that NIAID report by February 28, 2006 on the management of the consortium, as well as its plans for future research in the field. (p. 76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is deeply committed to supporting research efforts aimed at understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases. To this end, in fiscal year (FY) 2003 the NIAID, with support from the National Institute of Child Health and Human Development, established the U.S. Immunodeficiency Network (USIDNET), an international coalition of the most prominent researchers in the field of primary immunodeficiency diseases. Since its inception, the consortium has helped to prioritize and coordinate research directions in the area of primary immunodeficiency diseases and develop new resources for the study of these comparatively rare disorders. The mission of USIDNET is to form a cooperative network of primary immunodeficiency disease investigators; establish an award mechanism for peer-reviewed small, short-term projects for innovative studies; provide leadership and mentoring for clinical and basic investigators new to the field; enhance the primary immunodeficiency diseases registries currently supported by the National Institutes of Health; and establish a repository for samples from individuals affected by primary immunodeficiency diseases.

The USIDNET is governed by a ten-member Steering Committee that provides leadership to the Consortium and establishes Consortium policies and procedures. In addition, the Steering Committee enhances the coordination of primary immunodeficiency diseases research effort by identifying research gaps and opportunities, mechanisms by which to foster more research on primary immunodeficiency diseases, and methods to encourage new investigators to enter this field. The Steering Committee leads USIDNET through regular monthly teleconferences and biannual meetings.

The Steering Committee also solicits proposals and makes awards, via pilot and small research projects on primary immunodeficiency diseases. A peer-review advisory panel, the Grant Review Committee, meets by teleconference three times annually to review and evaluate research proposals and make funding recommendations to the Steering Committee. Typical awards are for two years, with a total award of $250,000 - $300,000 over the award period. Research areas supported by USIDNET include clinical, immunologic, and molecular characterization of genetically determined immunodeficiency diseases; determination of the molecular bases of newly defined primary immunodeficiency diseases; development of improved diagnostic tools for

primary immunodeficiency diseases; development of novel therapeutic approaches for primary immunodeficiency diseases; and utilization of the primary immunodeficiency diseases registries, and DNA and cell repository. As of October 2005, 45 full applications have been submitted to the USIDNET and, of these, 16 grant awards have been made.

In its efforts to provide leadership and mentoring for clinical and basic investigators new to the field, the USIDNET has established a Mentoring Committee to support several programs. For example, the Summer School program for fellows and junior faculty provides training on the diagnosis, pathogenesis, and treatment of primary immunodeficiency diseases and aims to attract and develop future scientists in academic medicine and to enhance the awareness of clinical immunology and its importance in scientific discoveries and clinical application to human diseases. The Committee also makes awards for travel to and attendance at national and international scientific meetings with sessions devoted to primary immune deficiency diseases and supports an elective awards program to facilitate the learning of new techniques and to provide clinical experiences to new investigators.

The USIDNET established a repository for samples from individuals affected by primary immunodeficiency diseases as well as a related patient data registry; diseases currently included in the repository are X-linked Agammaglobulinemia, Severe Combined Immunodeficiency Disease, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, X-Linked Hyper IgM Syndrome, Chronic Granulomatous Disease, DiGeorge Anomaly, and Leukocyte Adhesion Defect. Approximately 1,500 patients with these disorders have been registered to date. Each disorder has a Scientific Advisory Subcommittee that provides oversight and has the authority to approve the use of registry information for scientifically meritorious reasons. The registry is operated in compliance with the Health Insurance Portability and Accountability Act of 1996. Future plans for the repository and registry include implementation of an electronic clinical data entry system with remote data entry; tiered access to the database available to the general public and approved investigators; and education of physicians and researchers on the availability of the samples for independent research.

Item

Psoriasis - The Committee encourages NIAID to support research on psoriasis, a chronic, immune-related disease that affects between 5.8 and 7.5 million Americans. Safe and effective treatments for women of child-bearing age and for children are particularly lacking, and new research indicates mothers with psoriasis have a 50% increased risk of bearing a child with autism. The Committee asks NIAID to investigate the possible causes of this troubling finding, as well as related research on causes of and treatments for psoriasis. (p. 76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports the Immune Tolerance Network (ITN) to evaluate novel, tolerance-inducing therapies in autoimmune diseases, asthma, and allergic diseases; and to prevent rejection of transplanted organs, tissues, and cells. Through the ITN, the NIAID has recently initiated enrollment of patients in a clinical trial, "Treatment of Psoriatic Arthritis (PSa) with hOKT3λ1 (Ala-Ala)." The primary clinical objective of the study is to determine the safety and clinical efficacy of hOKT3γ1 (Ala-Ala) in combination with methotrexate or azathioprine in the treatment of psoriatic arthritis.

In addition, the NIAID supports a cooperative research group, "HLA Region Genetics in Immune-Mediated Diseases," to define the association between human leukocyte antigen region genes or genetic markers and immune-mediated diseases such as psoriasis.

In fiscal year 2007, the NIAID plans to re-compete the Immune Tolerance Network. Autoimmune diseases, including psoriasis, will remain an important component of NIAID's research portfolio. The Institute will continue to support research into psoriasis, its possible causes and complications, and potential treatment and prevention strategies.

NIAID research focuses on the immunology of psoriasis and does not include investigations into the possible links between maternal psoriasis and autism. The National Institute of Mental Health, another component of the National Institutes of Health (NIH), supports research into the association of pregnancy and birth complications with autism and other severe mental disorders, which could provide evidence of associations between maternal health during pregnancy and autism. The autism research matrix produced by the Interagency Autism Coordinating Committee in 2004 calls for research that will identify environmental factors, including maternal health, contributing to autism. The NIH will continue to pursue such research.

Item

Transplantation Research –The Committee is aware that while one-year organ transplantation survival has improved remarkably over the last fifteen years, there has been little success in reversing the decline in long-term graft and patient survival. The Committee suggests that NIAID convene an expert conference, in collaboration with NIDDK and NHLBI, to develop a five-year Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The expert conference should also focus on promising new technologies in pre-transplant organ care and post-transplant patient therapies. The Committee also suggests the initiation of a cohort study to assess the health outcomes of living donors, not only for the period immediately following the donation, but for the quality of life implications in the decades post-donation. (p. 75-76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues to pursue research initiatives to advance scientific understanding of the immunology of transplantation, to understand the critical role of immune tolerance in organ graft survival, and to improve long-term outcomes for transplant patients.

For example, current immunosuppressive medications necessary for the survival of transplanted organs or tissues can often result in systemic hypertension, diabetes mellitus, renal insufficiency, and malignancy in solid organ transplant recipients. Through initiatives such as the NIAID-supported Immune Tolerance Network (ITN), researchers are evaluating novel, tolerance-induction strategies and how the induction of tolerance can prevent rejection of transplanted organs, tissues, and cells, including kidney, liver and islet cells. The ITN is co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International.

In September 2005, the NIAID convened a panel of experts in transplant surgery and immunology to review current research in the field of transplantation and to develop recommendations for future research needed to improve graft acceptance and post-transplant quality of life. The recommendations of the expert panel will be published in a five-year action plan, which is anticipated to be completed in late spring 2006.

The NIAID also supports basic and clinical research in organ transplantation. For example, the Clinical Trials in Organ Transplant Consortium, initiated in fiscal year (FY) 2004, is a five-year program to define a scientific agenda for clinical research in organ transplantation and implement collaborative, multi-center clinical trials with associated basic studies in the immune system mechanisms involved in organ transplantation. This initiative is co-sponsored by the NIDDK and the National Heart, Lung and Blood Institute.

In FY 2006, the Institute will support a program, Outcomes of Live Organ Donors, which will consist of a consortium of investigators who will conduct epidemiologic research on the outcomes and health needs of live organ donors. The investigators in this consortium will study individuals who have donated a kidney or a lobe of lung for transplantation.

Item

Tuberculosis - The WHO estimates that nearly 1 billion people will become infected with TB, 200 million will become sick, and 70 million will die worldwide between now and 2020 of this disease. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine. The Committee encourages the Institute to continue its TB vaccine development and to strengthen efforts to develop new drugs to treat TB. (p. 76)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID), through its Tuberculosis (TB) Program, supports research on *Mycobacterium tuberculosis* (Mtb), the causative agent of TB, and how the body responds to this pathogen, and conducts clinical trials to translate this research into improved health care interventions. The focus of the TB Program is to develop drugs that will shorten and simplify TB therapy and to develop vaccines that will protect against all forms of TB.

The currently-available bacillus Calmette-Guerin (BCG) vaccine provides some protection against complications of TB in children but does not reliably prevent the development of contagious pulmonary TB in adults. Translational studies to improve upon the BCG vaccine are being conducted at the NIAID's Vaccine Treatment and Evaluation Unit (VTEU) in St. Louis, Missouri. The VTEU will conduct a Phase I clinical trial of primary and secondary BCG vaccination in healthy adults to whom the vaccine is delivered intradermally, orally, and by combined routes of administration. Enrollment of volunteers in this trial is expected to begin shortly.

A key component of the NIAID's successful contribution to TB vaccine development is its TB Research Materials and Vaccine Testing contract. This contract provides exploratory and preclinical evaluation of promising new TB vaccine candidates in animal models, thereby providing an interface between basic and applied science. More than 150 new TB vaccine candidates have been tested under this contract. One of these, Mtb72f, which was developed by Corixa Inc. in collaboration with GlaxoSmithKline, has recently entered human clinical trials.

NIAID-supported scientists have also developed many promising new anti-TB drug candidates. The NIAID partnered with the Global Alliance for TB Drug Development for the advanced development of a novel antibiotic, PA-824. This drug, which may shorten the time needed to treat both drug-sensitive and multi-drug-resistant TB, has begun testing in humans. In addition, the NIAID's Challenge Grant Programs have supported the pre-clinical development of SQ109, a derivative of the known anti-TB drug ethambutol. SQ109 may enter Phase I human clinical trials in 2006.

The NIAID-supported Tuberculosis Research Unit (TBRU) recently completed data analysis from a Phase II study in Uganda of a therapeutic, Proleukin®, in non-HIV-infected adults with pulmonary TB. The TBRU is currently enrolling subjects for a number of additional clinical trials to evaluate improved TB drug regimens. The TBRU contract will be re-competed in fiscal year (FY) 2007 and will continue to support the conduct of clinical research on TB.

The Institute's TARGET--Tuberculosis Animal Research and Gene Evaluation Taskforce--contract supports research to evaluate, in animal models, the biological function of Mtb gene products for their utility as drug, vaccine or diagnostic targets. A collection of mutant Mtb strains that were developed under the contract are provided to the research community upon request; 81 mutants were distributed through FY 2005.

Support for investigator-initiated basic and translational research on TB will remain a priority for the NIAID, adding to our knowledge base about Mtb and the pathogenesis of TB, and leading to the development of improved diagnostic, therapeutic and intervention strategies for combating TB. The NIAID will continue to support the discovery of new, more effective, selective therapeutic agents to treat and prevent TB through contracts, solicited and investigator-initiated grants, and Small Business Innovation Research/Small Business Technology Transfer mechanisms.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Asthma - The Committee is very pleased with NIAID's leadership regarding asthma research and management. 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 play in the development of asthma. (p.117)

Action taken or to be taken

Please refer to page 35 of this document for NIAID's response to this significant item regarding asthma.

Item

Atopic Dermatitis - The Committee was pleased to learn about NIAID research efforts related to atopic dermatitis undertaken through projects such as the Immune Tolerance Network and the Atopic Dermatitis and Vaccinia Immunization Network. Last year, the Committee encouraged NIAID to complement these efforts by working with NIAMS to spearhead a multidisciplinary, multi-institute initiative to encourage investigator-initiated research projects on AD as it relates to smallpox vaccination as well as the progression to asthma and other allergic diseases. The Committee requests an update in the fiscal year 2007 appropriations justification on efforts that have been made to foster investigator-initiated research in this area. (p. 117)

Action taken or to be taken

Atopic dermatitis is one of the most common skin diseases and is frequently associated with other allergic diseases and asthma. The National Institute of Allergy and Infectious Diseases (NIAID) and other National Institutes of Health (NIH) Institutes and Centers

support a broad range of investigator-initiated research on skin and skin diseases, including atopic dermatitis.

For example, the NIAID supports an investigator-initiated mechanistic study associated with a clinical trial to determine if the non-steroidal immunomodulatory drug pimecrolimus will prevent progression to asthma in young children with atopic dermatitis.

In addition, the NIAID-supported Immune Tolerance Network (ITN) is developing clinical trials to determine if oral administration of cat, grass, and house dust mite allergens will prevent the development of allergic diseases and asthma in children with atopic dermatitis and food allergy. The ITN is also developing a trial to investigate whether feeding a peanut-containing snack to young children at risk of developing peanut allergy will prevent development of this allergy; all patients enrolled in this trial will have atopic dermatitis or allergy to eggs.

Persons with atopic dermatitis are at risk of a severe skin rash, called eczema vaccinatum, in response to the currently-available Dryvax ® smallpox vaccine. In fiscal year (FY) 2004, the NIAID, with expert advice and support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), established the Atopic Dermatitis and Vaccinia Immunization Network to develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum and to protect individuals with atopic dermatitis from the adverse consequences of smallpox vaccine exposure. In addition, the NIAID supports research to develop a vaccine with fewer side effects. In FY 2004, the NIAID continued its support of advanced development and manufacture of modified vaccinia Ankara (MVA) vaccine for smallpox by awarding two new contracts. These contracts specify that contractors conduct Phase I and II trials to determine the safety and immunogenicity of MVA in participants with diagnosed atopic disorders.

The NIAID will continue to support research into the cause, treatment, and eventual cure of atopic dermatitis. In FY 2007, the NIAID will establish the Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases program to identify novel allergens and reagents to facilitate the development of therapeutic strategies to treat and prevent allergies. In addition, the NIAID will continue to support MVA-based vaccine research and development, with the goal of developing a smallpox vaccine that can be used safely in all populations who are at risk for complications from the current smallpox vaccine.

Item

Autoimmune Diseases - The Committee applauds the formation of two cooperative research groups, the Autoimmune Centers of Excellence and the Cooperative Study Group for Autoimmune Disease Prevention, which support multidisciplinary research to understand and treat autoimmune diseases. The Committee urges NIAID to continue its support for the prevention centers and to encourage the participation of the wider research community in this initiative. (p. 117)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues to support and foster multidisciplinary research to better understand and treat autoimmune diseases. The NIAID, along with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), supports the Autoimmunity Centers of Excellence to conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials and mechanistic studies of immunomodulatory therapies.

The NIAID also supports the Autoimmune Diseases Prevention Centers, which conduct research on the development of new targets and approaches to prevent autoimmune diseases and evaluate these approaches in pilot and clinical studies. In fiscal year (FY) 2005, the Prevention Centers supported 22 pilot projects that may lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression. The Prevention Centers are co-sponsored by NIDDK, the National Institute of Child Health and Human Development (NICHD), ORWH, and the Juvenile Diabetes Research Foundation International (JDRF). The Institute will renew the Autoimmune Diseases Prevention Centers in FY 2006.

In addition, the NIAID supports other collaborations and consortia that conduct research into autoimmune diseases. The Immune Tolerance Network, co-sponsored by the NIDDK and JDRF, evaluates novel, tolerance-induction strategies and their mechanisms of action in autoimmune diseases. The Multiple Autoimmune Diseases Genetics Consortium is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. The repository provides material to qualified researchers for use in research to identify genes involved in autoimmune diseases.

Item

Bioterrorism - Respiratory pathogens that cause life-threatening pneumonia are commonly proposed agents of bioterrorism. The following are associated with acute pneumonia/lung injury: anthrax, smallpox, plague, and tularemia. The Committee encourages further research on the mechanisms of pneumonia by these respiratory pathogens and the development of new therapeutic interventions to reduce injury and death. (p. 117)

Action taken or to be taken

Please refer to page 36 of this document for NIAID's response to this significant item regarding bioterrorism.

Item

Coinfection Research – The Committee is concerned that there is growing evidence of liver toxicity of highly active antiretroviral therapy (HAART) in those with chronic viral hepatitis and in particular those with decompensated liver disease awaiting liver transplantation. There also appears to be an emerging problem of liver cancer in co-infected patients (HCV and/or HBV with HIV). The Committee encourages NIAID to initiate significant research initiatives in both of these areas. (p. 117)

Action taken or to be taken

Please refer to pages 3-4 of this document for NIAID's response to this significant item regarding coinfection research.

Item

Hemophilia – The Committee urges NIAID to continue its efforts to develop and advance research initiatives for addressing HCV within the bleeding disorders community. The Committee understands that HCV continues to have a devastating impact on this community, with nearly half of all persons with hemophilia having contracted HCV from blood clotting factor products. (p. 118)

Action taken or to be taken

Please refer to pages 8-9 of this document for NIAID's response to this significant item regarding hemophilia.

Item

Hepatitis – The Committee continues to be concerned about the prevalence of hepatitis and urges NIAID to work with public health organizations to promote liver wellness, education, and prevention of hepatitis. (p. 118)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to the reduction of the burden of disease caused by hepatitis. The NIAID continues to further awareness of hepatitis by organizing and participating in conferences on hepatitis and by providing easily accessible information on hepatitis.

The NIAID has supported two National Institutes of Health (NIH) Consensus Development Conferences focused on the management of hepatitis C disease. Held in 1997 and 2002, the purpose of these conferences was to evaluate the available scientific information on hepatitis and to develop a consensus statement that advances the understanding of hepatitis among health professionals and the public. In addition, NIAID investigators and program staff frequently participate in scientific workshops and meetings to discuss critical issues in basic hepatitis research and disease management.

For example, NIAID extramural program staff recently met with representatives of the National Hemophilia Foundation to discuss ways in which the Foundation's constituency, in which there is a prevalence of infection with hepatitis C virus, might participate in NIAID-supported clinical trials.

NIAID also provides information on publications, research breakthroughs and disease management resources on the Institute's web site. This information includes links to resources on hepatitis disease management available through NIAID and other NIH Institutes. For example, information on hepatitis which is available through the National Institute of Diabetes and Digestive and Kidney Diseases is accessible through the NIAID web site.

The NIAID will continue to promote prevention of hepatitis through these efforts and through continued support of investigator-initiated research on hepatitis; applied research and development efforts through partnerships with academic and corporate scientists; clinical trials and ancillary research using NIAID-supported cooperative agreements and contracts.

Item

Hepatitis C Vaccine Development - The Committee is encouraged to learn that a small hepatitis C vaccine human trial has been successfully completed. The Committee urges NIAID to implement the results of the recent workshop that was held to discuss and evaluate efforts toward development of HCV vaccines with the goal of spurring their development and testing. The Committee also urges NIAID to proceed with phase two of the human clinical trial as soon as it is scientifically practicable. Additionally, NIAID is urged to foster the development of an in vitro culture system for HCV as well as new animal models for basic research and for adequately testing vaccine candidates and antiviral drugs. (p. 118)

Action to be taken

Progress toward the development of a vaccine against hepatitis C virus (HCV) and reduction in the prevalence of this disease continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID plays a key role in hepatitis C research efforts across the National Institutes of Health (NIH). These trans-NIH efforts include a broad range of research activities in support of vaccine development, including basic research on HCV that guides vaccine development, studies that define potential population groups in which vaccines could be evaluated, the development of both preventive and therapeutic vaccines, and preclinical evaluation and clinical trials of vaccine candidates.

In 2004, the Institute launched a Phase I trial to evaluate the safety, tolerability, and immunogenicity of a candidate HCV vaccine. This trial is being conducted in the NIAID's Vaccine and Treatment Evaluation Units (VTEU) and is ongoing. The NIAID

is currently working with two companies to develop two additional Phase I trials of HCV vaccine candidates; these trials will also be conducted at VTEU sites.

In February 2005, the NIAID held a workshop on HCV vaccines which provided a forum for the comprehensive review of progress towards the development of vaccines for HCV. Scientists from academic institutions, pharmaceutical companies, biotechnology companies, and Federal government agencies participated in this review of HCV vaccine research efforts including the latest advances in research, the epidemiology of HCV, the immunological parameters important in vaccine development, and candidate vaccines which are currently in development.

In response to the suggestions stemming from this workshop, the NIAID developed the initiative Partnerships for Hepatitis C Vaccine Development, which will be supported in fiscal year 2006. The purpose of this initiative is to stimulate the development of vaccines against HCV infection and the chronic conditions that result from HCV infection. Research may include the design and construction of vaccines, preclinical evaluation of vaccine candidates, and pilot scale manufacture of vaccine candidates.

The NIAID recognizes the need for a cell culture system for HCV. The NIAID has helped to support a collaborative effort involving Rockefeller University, the Massachusetts Institute of Technology and the Scripps Research Institute to produce a tissue culture cell line in which the entire HCV replicates. This development will allow further investigation into the life cycle of the virus and provides a tool for screening new therapies and testing vaccine candidates.

The NIAID is also pursuing the development of new animal models for HCV research. The Institute is supporting research toward these new animal models through the initiative, Animal Models for the Prevention and Treatment of Hepatitis B and Hepatitis C. In addition, NIAID investigators are working to develop an animal model for HCV. Toward this end, they are studying infection of the tamarin with GB virus B, a close relative of HCV, as a model for hepatitis C infection in humans.

Item

Infectious Disease Research- The Committee believes that, with regard to both biodefense and public health, the development by NIAID of multi-pathogen identification arrays that can be used to identify infectious agents through epidemiological outbreak surveillance is critically important. The use of whole genome expression, all exon transcription analysis and whole genome SNP analysis studies to identify and understand host biomarkers that may identify the type, severity and likely response to therapeutics of infectious agents hold great promise for the most immediate results. The Committee encourages NIAID to pursue these lines of inquiry. (p. 119)

Action taken or to be taken

Please refer to pages 7-8 of this document for NIAID's response to this significant item regarding genetic tools for infectious disease research.

Item

Immune Surveillance Cell Proteomes- The Committee recognizes the potential threat to national security posed by terror attacks involving biological, chemical, nuclear, and radiological weapons. One of the challenges facing public health officials responding to such an attack is their limited ability to diagnose individuals who have been exposed to these agents and do not show illness. Recent disease outbreaks—such as SARS in Asia and Canada, avian influenza in East Asia, and Ebola and Marburg virus in Africa—demonstrate that the speed of diagnosis and implementation of public health measures can mean the difference between an isolated outbreak and a global pandemic. Therefore, the Committee strongly supports research on immune surveillance cell proteomes (e.g. monocytes, neutrophils, dendritic cells, B cells and NK cells) and their response to chemical and biological pathogens. The Committee also urges the NIAID to fund the development of a searchable electronic database for biological proteomes, the proteomics of immune surveillance cell interaction with pathogens (biological and chemical), and proteins derived from the immune surveillance cells themselves, as well as their interaction with pathogens. (p. 118)

Action taken or to be taken

Please refer to pages 5-6 of this document for NIAID's response to this significant item regarding immune surveillance cell proteomes for detection of disease and bioterror agents.

Item

Immune Tolerance – The Committee is encouraged by the progress of the Immune Tolerance Network in launching clinical trials of protocols to induce immune tolerance in patients with Type 1 diabetes. These trials have the potential to prevent the recurrence of autoimmunity in patients with long-standing diabetes who have undergone islet transplantation and halt the autoimmune attack in recently diagnosed Type 1 diabetes patients. The Committee encourages the NIAID to continue its strong support of this clinical network and to expand its clinical studies promoting the translation of promising basic discoveries. (p. 118)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) recognizes that advances in immune tolerance induction will provide valuable therapeutic strategies while eliminating the need for life-long, systemic immunosuppressive therapy with its deleterious side effects. Thus, the NIAID supports a broad range of basic, translational,

and clinical research on the underlying mechanisms of immune tolerance and the evaluation of tolerance induction strategies in animal models and clinical trials.

An example of the Institute's research efforts in this area is the Immune Tolerance Network (ITN), an international, collaborative research consortium co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International. Researchers of the ITN evaluate novel tolerance induction strategies and their mechanisms of action in the treatment of autoimmune diseases, asthma, and allergic diseases, and in the prevention of rejection of transplanted organs, tissues, and cells.

In addition, the NIAID supports the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) to develop novel approaches to tolerance induction and to evaluate the safety and efficacy of tolerogenic regimens in non-human primate models of kidney and islet transplantation. The NHPCSG, cosponsored by NIDDK, was expanded in 2005 to include heart and lung transplantation models.

The NIAID, along with the NIDDK and the National Heart, Lung, and Blood Institute, supports the Innovative Grants on Immune Tolerance program to conduct pilot research projects on the molecular mechanisms and applications of antigen-specific immune tolerance. Also, with co-sponsor NIDDK, the NIAID supports the Immunobiology of Xenotransplantation program to develop pre-clinical porcine to non-human primate models of xenotransplantation.

In fiscal year (FY) 2006, the NIAID will renew the Innovative Grants on Immune Tolerance program. In FY 2007, NIAID will renew the NHPCSG program and re-compete the ITN. Through continuing support of these programs, the NIAID will maintain its commitment to basic research on immune tolerance and the translational and clinical research that bring basic discoveries to the patient care arena.

Item

Inflammatory Bowel Disease –The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) titled ''Challenges in Inflammatory Bowel Disease [IBD].'' This report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to expand its research partnerships with the IBD community in fiscal year 2006 and increase funding for research focused on: (1) the immunology of IBD and (2) the interaction of genetics and environmental factors in the development of the disease. (p. 119)

Action taken or to be taken

Please refer to pages 9-10 of this document for NIAID's response to this significant item regarding inflammatory bowel disease.

Item

Lupus - The Committee recognizes that Lupus is a serious, complex, debilitating chronic autoimmune disease that causes inflammation and tissue damage to virtually any organ system in the body and impacts between 1.5 and 2 million individuals. The Committee strongly urges the National Institute of Allergy and Infectious Diseases to expand and intensify research and related activities with respect to Lupus. (p. 119)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) maintains its commitment to developing better diagnosis, treatment, and prevention strategies for lupus, one of a group of autoimmune diseases that disproportionately affect women and minorities.

Through the Immune Tolerance Network (ITN), the NIAID is currently evaluating a new potential treatment for lupus. The ITN is conducting a Phase II clinical trial of a two-drug combination consisting of a compound that may turn off the body's inappropriate autoimmune response and a second drug known to have chemotherapeutic effects. The ITN also conducts other studies to evaluate novel, tolerance-inducing therapies in autoimmune diseases. The ITN program will be re-competed in fiscal year (FY) 2007.

The nine Autoimmunity Centers of Excellence (ACE), which are co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multi-site clinical trials of immunomodulatory therapies. The ACEs support close interaction between clinicians and basic researchers, which should facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. Examples of ACEs-supported clinical trials include a Phase I/II clinical trial of anti-CD20 for treatment for lupus that is currently open for enrollment and a Phase I clinical trial of anti-TNF for treatment of lupus nephritis that is in development.

The NIAID, along with the NIDDK, the National Institute of Child Health and Human Development, the ORWH, and the Juvenile Diabetes Research Foundation International (JDRF), supports the Autoimmune Disease Prevention Centers to conduct research on the development of new targets and approaches to prevent autoimmune diseases, including lupus. This program will be renewed in FY 2006.

The NIAID also supports to the Multiple Autoimmune Diseases Genetics Consortium, a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This repository provides specimens and data to scientists who conduct research to identify genes involved in autoimmune diseases.

In FY 2007, the NIAID plans to support a new initiative, "Allogeneic Hematopoietic Stem Cell Transplantation for Autoimmune Diseases," to evaluate the effectiveness of hematopoietic stem cell transplantation to halt progression or even cure patients with autoimmune diseases, such as lupus. The initiative will also provide valuable data on the pathophysiological mechanisms of autoimmune diseases.

The NIAID coordinates its lupus research activities with other NIH Institutes and Centers and with other Federal agencies through participation in the Lupus Federal Working Group and the Autoimmune Diseases Coordinating Committee (ADCC). The NIAID chairs the ADCC, which submitted its most recent report to Congress in March 2005.

Item

Psoriasis - Psoriasis is a common, chronic, immune-mediated skin disease. The Committee urges NIAID to support additional research on psoriasis and psoriatic arthritis pathogenesis, research to develop diagnostic tests for psoriatic arthritis and clinical research to identify new safe and effective therapies for these diseases. (p. 119)

Action taken or to be taken

Please refer to pages 16-17 of this document for NIAID's response to this significant item regarding psoriasis.

Item

Tuberculosis - The World Health Organization [WHO] estimates that nearly one-third of the world's population will become infected with tuberculosis [TB]; and by 2020, 70 million people will die worldwide of this disease. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine. The Committee encourages the Institute to continue its TB vaccine development work and expand efforts to develop new drugs, including multi-drug resistant drugs to treat TB. (p. 120)

Action taken or to be taken

Please refer to pages 18-20 of this document for NIAID's response to this significant item regarding tuberculosis.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$4,324,901,000	Indefinite	$4,337,386,000
Infectious Diseases	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	58,400,000		58,110,000
Total, Budget Authority				4,383,301,000		4,395,496,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

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/
1998	634,272,000 2/	1,339,459,000	1,359,688,000	(1,351,655,000)
1999	703,723,000 2/ 3/	1,470,460,000	1,540,102,000	1,570,102,000
Rescission	0	0	0	(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	4,335,155,000
Rescission				(30,593,000)
2005	4,440,007,000	4,440,007,000	4,456,300,000	4,440,007,000
Rescission				(37,166,000)
2006	4,459,395,000	4,459,395,000	4,547,136,000	4,427,895,000
Rescission				(44,594,000)
2007	4,395,496,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research
3/ Reflects a decrease 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 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	280	268	280
Division of Allergy, Immunology, and Transplantation	71	68	71
Division of Microbiology and Infectious Diseases	135	129	135
Division of Extramural Activities	157	150	157
Division of Acquired Immunodeficiency Syndrome	126	120	126
Division of Intramural Research	780	780	782
Total	1,549	1,515	1,551
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(19)	(19)	(19)

FISCAL YEAR	Average GM/GS Grade
2003	11.4
2004	11.4
2005	11.4
2006	11.6
2007	11.6

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	0	0	0
Total - ES Salary	$0	$0	$0
Subtotal	0	0	0
Total - ES Salary	$0	$0	$0
GM/GS-15	75	75	75
GM/GS-14	227	226	229
GM/GS-13	219	214	219
GS-12	181	172	181
GS-11	179	170	179
GS-10	3	3	3
GS-9	96	93	96
GS-8	35	32	35
GS-7	72	69	72
GS-6	22	22	22
GS-5	9	8	9
GS-4	3	3	3
GS-3	2	2	2
GS-2	2	2	2
GS-1	2	2	2
Subtotal	1,127	1,093	1,129
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	18	18	18
Senior Grade	18	18	18
Full Grade	3	3	3
Senior Assistant Grade	1	1	1
Assistant Grade			
Subtotal	41	41	41
Ungraded	429	429	429
Total permanent positions	1,179	1,153	1,180
Total positions, end of year	1,597	1,561	1,598
Total full-time equivalent (FTE) employment,end of year	1,549	1,515	1,551
Average ES salary	$0	$0	$0
Average GM/GS grade	11.6	11.6	11.6
Average GM/GS salary	$76,162	$78,523	$80,251

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

New Positions Requested

	FY 2007		
	Grade	Number	Annual Salary
ADMINISTRATIVE ASSISTANT	12	1	65,048
BUDGET ANALYST	11	1	54,272
BUDGET ANALYST	12	1	65,048
CONTRACT SPECIALIST	11	2	54,272
FINANCIAL TECHNICIAN	8	1	40,612
HEALTH SCIENCE ADMINISTRATOR	11	4	54,272
HEALTH SCIENCE ADMINISTRATOR	12	3	65,048
HEALTH SCIENCE ADMINISTRATOR	13	1	77,353
INTERNATIONAL PROGRAM SPECIALIS	14	1	91,407
MANAGEMENT ANALYST	12	1	65,048
MATHEMATICAL STATISTICIAN	13	1	77,353
MEDICAL OFFICER	13	2	77,353
MEDICAL OFFICER	14	1	91,407
OFFICE AUTOMATION	5	1	29,604
OPERATIONS RESEARCH ANALYST	12	1	65,048
OPERATIONS RESEARCH ANALYST	14	1	91,407
PROGRAM ANALYST	9	3	44,856
PROGRAM ANALYST	11	2	54,272
PROGRAM ANALYST	12	2	65,048
PROGRAM ANALYST	13	1	77,353
PURCHASING TECHNICIAN	7	1	36,671
RECORDS MANAGEMENT TECHNICIAN	8	1	40,612
SECRETARY	7	2	36,671
SECRETARY	8	1	40,612
Total Requested		36	