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 13 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

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

of bioterror, include: anthrax, smallpox, plague, botulism, tularemia, and viral hemorrhagic 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 threats 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 13). 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 it is 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 by providing infectious disease experts as part of a national network to augment the NIH consultation call center. 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 six-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 ten 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 WNV. 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 Re-emerging 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 in the avian population to over 16 countries. As of January 30, 2006, there have been 160 confirmed cases in humans with 85 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 were 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 candidate is 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, and 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 ongoing 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 enhance 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 are 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 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 a person

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)

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 governmental and non-governmental 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. To date, there are a total of ten CHAVI clinical sites located in Malawi, South Africa, Uganda, Tanzania, and England, and the United States, including sites in North Carolina, Alabama, and Massachusetts. In early 2006, four additional South African institutions will join the CHAVI effort. Several clinical protocols currently are under development, including ones that will examine the host immune response to HIV and one that will examine genetic predisposition to HIV infection. Additional information about CHAVI is available at www.chavi.org.

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, 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 contain 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. The trials will 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 *M. tuberculosis* protein targeted by PA-824, which may help scientists streamline the approach for optimizing this promising drug.

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

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.

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. NIAID has 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) (see page 19) 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.

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)

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. Their finding showed that the loss of these cells is extensive 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

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 the first evidence that the virus uses a human enzyme known as DDX3 to straighten its RNA before threading it through a small pore in 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 *P. falciparum*. 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 confers 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

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

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.

NIAID directs the Autoimmune Diseases Coordinating Committee (ADCC), which was established by NIH in 1998, and is composed 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 bases 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

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

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)

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 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 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.

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

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 composed 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 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

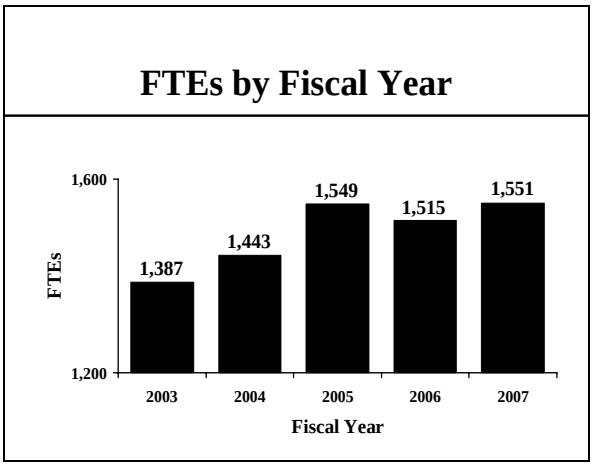
collaborative research groups. These types of research teams are needed to implement many biodefense initiatives including, for example, the Partnerships for Biodefense, for extramural grantees, as well as the Trans-NIH/FDA Intramural Biodefense Program.

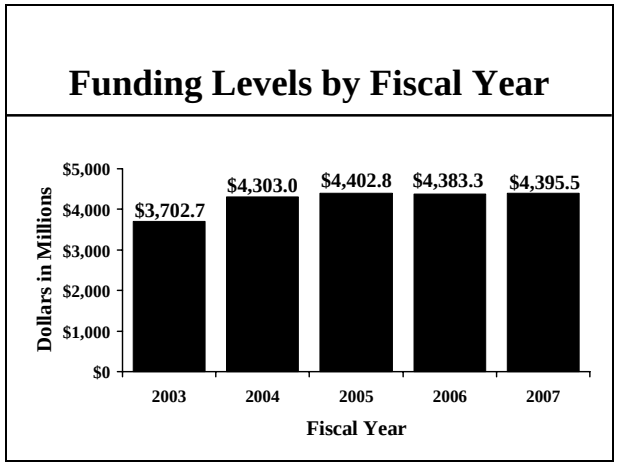
The planning and implementation grants for Institutional Clinical and Translational Science Awards will support NIAID's efforts to improve clinical research, particularly in the context of advanced product development. These activities are intended to increase the speed with which new knowledge moves 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 $4,395,496,000, 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 percent 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 are 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.

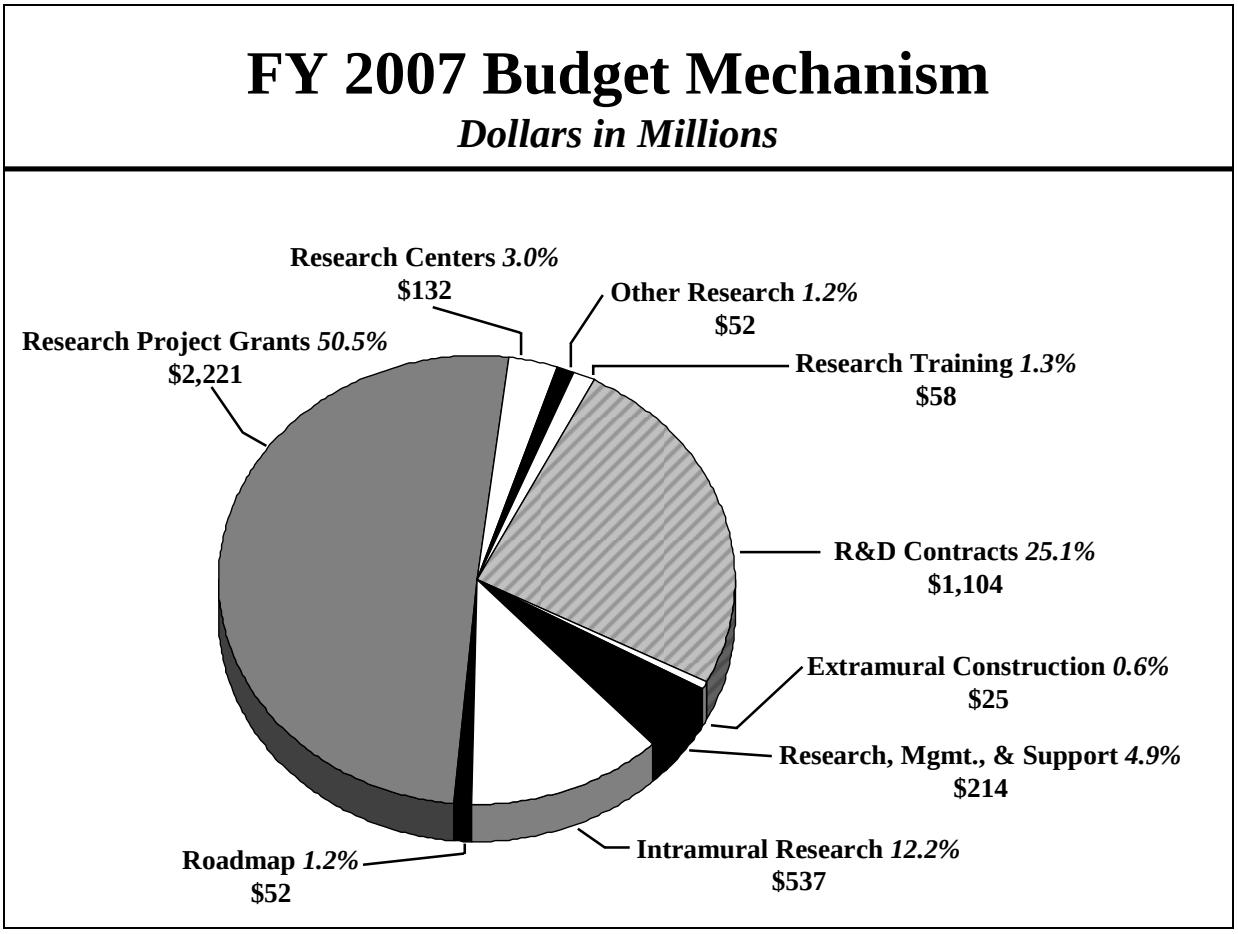
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIAID, $540,000 will be used to support six awards for the new K/R "Pathway to Independence" program. NIAID will also support the 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 Estimate
Percent Change from FY 2006 by Mechanism