DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2007 Budget Request

Witness appearing before the
House Subcommittee on Labor-HHS-Education Appropriations

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Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The Fiscal Year (FY) 2007 budget of $4,395,496,000 includes an increase of $12,195,000 over the FY 2006 appropriated level of $ 4,383,301,000, comparable for transfers proposed in the President's request.

The mission of NIAID is to conduct and support research to understand, treat, and prevent infectious and immune-related diseases. Infectious diseases include well-known killers such as HIV/AIDS, malaria, and tuberculosis; emerging or re-emerging threats such as influenza; and "deliberately emerging" threats from potential agents of bioterrorism. Immune-related disorders include autoimmune diseases such as type 1 diabetes and rheumatoid arthritis as well as asthma, allergies, and problems associated with transplanted tissues and organs.

NIAID has a two-fold mandate. First, NIAID must plan and execute a comprehensive and long-term basic and clinical research program on well-recognized endemic infectious and immune-mediated diseases. Second, and in this case it is unique among the NIH Institutes, it must respond quickly with targeted research to meet new and unexpected infectious disease threats as they arise, often in the form of public health emergencies. Part of the expansion of the NIAID research portfolio in recent years has been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of microbiology and immunology. 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. But the scope of NIAID

programs also has grown because of a growing realization that biomedical research is a key component of a successful response to new challenges posed by emerging and re-emerging infectious diseases such as pandemic influenza and HIV/AIDS, the threat of bioterrorism, and the increase in asthma prevalence among children.

EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Despite advances in medicine and public health such as antibiotics, vaccines, and improved sanitation, the World Health Organization (WHO) estimates that infectious diseases still account for approximately 26% of all deaths worldwide, including about two-thirds of all deaths among children younger than five years of age. Moreover, the pathogens we face are not static, but change dramatically over time as new microbes emerge and familiar ones re-emerge with new properties or in unusual settings.

Influenza is perhaps the most pertinent example of a re-emerging disease. Influenza viruses continually accumulate small changes such that a new vaccine must be made for each influenza season. When a totally new influenza virus against which the global population has no natural immunity emerges, a worldwide pandemic can result if the new viruses are able to transmit efficiently between people. Three such pandemics occurred in the 20th century, in 1918, 1957, and 1968. The pandemics of 1957 and 1968 were severe infectious disease events that killed approximately two million and 700,000 people worldwide, respectively. The 1918-1919 pandemic, however, was catastrophic. Public health experts estimate that the 1918 pandemic killed more than 500,000 people in the United States and more than 50 million people worldwide.

The highly pathogenic H5N1 avian influenza virus currently found in domestic and

migratory birds in Asia, Africa, the Middle East, and Europe is of great concern. Although H5N1 is primarily an animal pathogen, it nonetheless has infected more than 170 people; more than half of all confirmed H5N1 patients have died. At this time, the virus is not able to spread efficiently from animals to humans and is extremely inefficient in spreading from person to person, but the feared human influenza pandemic could become a reality if the H5N1 virus mutates further or mixes its genes with human influenza viruses, remains highly virulent, and acquires the capability to spread efficiently from person to person.

It is imperative that we prepare for the possibility that a new influenza virus will emerge to cause a 1918-like pandemic among human beings. It is important to note, however, that our ability to cope with a pandemic—with a sufficient supply of effective vaccines and antiviral drugs, effective infection control, and clear public communication—will to a large extent depend on how well we cope with seasonal influenza. It is clear that we have not yet optimized our preparedness and responsiveness to this recurring disease, which, according to estimates of the Centers for Disease Control and Prevention (CDC), kills an average of about 36,000 people in the United States each year. The serious vaccine shortage that occurred in the 2004/05 influenza season underscored the difficulties we face in annually renewing the influenza vaccine supply, and highlights the pressing need to move toward adoption of newer vaccine manufacturing techniques and other strategies that can improve the surge capacity, flexibility and speed with which vaccines are made.

NIAID supports numerous research projects that lay the foundation for improved influenza vaccine manufacturing methods, new categories of vaccines that work against

multiple influenza strains, as well as the next generation of anti-influenza drugs. Some of these are basic research projects intended to increase our understanding of how animal and human influenza viruses replicate, interact with their hosts, stimulate immune responses, and evolve into new strains. Other projects are more targeted, such as a program to screen compounds for antiviral activity against influenza viruses. One particularly important effort is to develop a vaccine that raises immunity to parts of the influenza virus that do not vary from season to season. Not only would such a vaccine provide continued protection over multiple influenza seasons, it might also offer considerable protection against a newly-emerged pandemic influenza virus and thereby substantially improve our preparedness for pandemic threats.

The Department of Health and Human Services (DHHS) Pandemic Influenza Response and Preparedness Plan designates NIAID as the lead agency for research and development efforts related to pandemic influenza. In this capacity, NIAID has developed and is clinically evaluating several candidate H5N1 vaccines, including inactivated and live-attenuated vaccines, as well as other strategies such as recombinant subunit and DNA vaccines. The potential benefits of NIAID research to the American public have been clear and immediate. The pre-pandemic H5N1 vaccine that is currently being stockpiled by DHHS was shown in clinical trials by NIAID to be safe and capable of inducing an immune response that would be predictive of being protective against the H5N1 virus. The dose of vaccine required for this protection, however, is high; and current NIAID studies are aimed at enhancing the response to lower doses of the H5N1 vaccine, particularly with the use of adjuvants, which are compounds that have been shown to enhance the immune response to vaccines. NIAID

also conducts surveillance for the molecular evolution of influenza viruses among animals and humans in Asia and elsewhere, and tracks changes in the virus that might allow it to be transmitted more easily among people. The Institute also is evaluating new antiviral drugs against H5N1 influenza as well as combinations and varied doses of existing drugs. In addition, NIAID is working to establish a clinical trials network in Southeast Asia to conduct research on emerging infectious diseases, with an initial emphasis on influenza.

Influenza is by no means the only emerging and re-emerging infectious disease threat that the world faces. For example, malaria is a substantial and growing problem compounded by the emergence of drug-resistant malaria parasites and insecticide-resistant mosquito vectors. NIAID supports a large malaria research portfolio; one recent study identified a specific parasite gene that is essential for full maturation of the parasites in mice. Disrupting this gene not only prevented the onset of disease in mice, but injection of the modified parasites stimulated an immune response that protected them from subsequent infection with unmodified, fully-virulent malaria parasites. This indicated that genetically attenuated parasites might be useful as a malaria vaccine in the future.

Tuberculosis (TB) is an example of a microbial disease that has reemerged in recent years. Infection with *Mycobacterium tuberculosis* is estimated to be prevalent in one-third of the world's population and is especially common among persons infected with HIV. NIAID supports a large portfolio of research to develop new drugs, vaccines, and diagnostics for TB and to evaluate improved treatment and preventive regimens. Recently, two novel, engineered TB vaccines developed with NIAID

support entered Phase I clinical trials in the United States. These promising candidates are the first new TB vaccines to be tested in people in more than 60 years. In addition, the Global Alliance for TB Drug Development and NIAID have collaborated to develop a promising new TB drug candidate, which is now being tested in clinical trials. NIAID also has made substantial research progress on West Nile Virus, multi-drug resistant tuberculosis (MDR-TB), SARS, and other new or re-emerging infections.

HIV/AIDS RESEARCH

HIV/AIDS was first recognized as an emerging disease only 25 years ago. Today it is a global catastrophe. According to the Joint United Nations Program on HIV/AIDS (UNAIDS), approximately 40 million people worldwide are living with HIV/AIDS, and their number is increasing by more than 5 million people every year—about 14,000 each day. In the United States, more than one million people are living with HIV/AIDS, and approximately 40,000 new infections occur annually. Worldwide, more than 25 million people with HIV have died since the pandemic began, including more than 520,000 in the United States. In 2004, there were 3 million deaths worldwide due to HIV/AIDS. These statistics are grim reminders of the physical and emotional devastation to individuals, families, and communities coping with HIV/AIDS, and of the terrible impact of HIV/AIDS on regional and global security and the global economy.

Development of a vaccine that protects against HIV/AIDS is one of the highest priorities of the NIAID. The scientific challenges that must be overcome, however, are extraordinary. Because the immune system, with rare exceptions, has not been shown to contain HIV on its own, an HIV vaccine will have to elicit an even stronger immune

response than elicited by natural HIV infection if it is to prevent infection. To help meet these challenges, NIAID established the Center for HIV/AIDS Vaccine Immunology (CHAVI) in June 2005. CHAVI's mission is to tackle the fundamental immunological obstacles in HIV vaccine research and to design, develop, and test novel HIV vaccine candidates. The establishment of CHAVI complements NIAID's continued support of other innovative research projects conducted through a highly cooperative and collaborative global research and development program.

Among many HIV vaccine research efforts, NIAID scientists have developed a two-part vaccination strategy, consisting of an initial (prime) vaccination followed by a later (boost) vaccination. The priming dose is a "naked" DNA vaccine, and the boost is a recombinant adenovirus vaccine, which is based on a highly attenuated version of a common cold virus. Both components contain genes from three different subtypes of HIV that together cause about 85 percent of all HIV infections around the world. An initial Phase I clinical trial showed that the pair of vaccines was well-tolerated and induced substantial immune responses. Building on these promising findings, NIAID recently launched a second phase of testing of this "prime-boost" strategy. This project is a collaboration between three international clinical trial networks—NIAID's HIV Vaccine Trials Network, the non-profit International AIDS Vaccine Initiative, and the U.S. Military HIV Research Program—and expands the safety and immunogenicity testing of the prime-boost strategy in the Americas, South Africa, and Eastern Africa. Also underway and slated to complete enrollment this year is the evaluation of a candidate adenoviral vaccine administered without a DNA vaccine to determine whether it may be useful alone in preventing HIV infection or disease.

The use of potent combinations of anti-HIV drugs, many of which were developed with NIAID support, has dramatically reduced the numbers of AIDS deaths in industrialized countries. Most recently these drugs have had a major impact on several developing countries in sub-Saharan Africa, the Caribbean, South America and Asia, as drugs have become available to them. Indeed, these drug regimens have transformed the complexion of HIV/AIDS throughout the world, saving the lives of millions of people. These results are some of the most cogent examples of the practical benefits of NIH-supported research. But we cannot be complacent in our success. Anti-HIV drug regimens often cause serious side effects and frequently lose their effectiveness due to the emergence of resistant forms of HIV within a patient. Clinical research is moving new classes of AIDS drugs closer to market and defining how to optimally use currently licensed medications. Basic HIV research continues to uncover additional viral and cellular targets for therapy. For example, several potential drug targets have been identified by determining the mechanisms that HIV uses to gain entry into host cells. These include fusion inhibitors, the first of which was recently approved by the Food and Drug Administration (FDA). In addition, several inhibitors of the HIV enzyme that allows the virus to enter and integrate into an infected cell's genes have shown great promise in clinical trials.

BIODEFENSE RESEARCH

The potential use of biological agents in a terrorist attack is a serious threat to the citizens of our nation and the world. Research to mitigate this threat is a key focus of NIAID. The NIAID Strategic Plan for Biodefense Research, developed shortly after the terrorist attacks of 2001, outlines three essential pillars of the NIAID biodefense

research program: *infrastructure* needed to safely conduct research on dangerous pathogens; *basic research* on microbes and host immune defenses that serves as the foundation for applied research; and targeted, milestone-driven development of *medical countermeasures* to create the vaccines, therapeutics and diagnostics that we would need in the event of a bioterror attack. Implementation of this plan enhances not only our preparedness for bioterrorism, but also for naturally occurring endemic and emerging infectious diseases. In addition, NIAID was recently given the role of coordinating and facilitating NIH research into countermeasures to mitigate harm to civilians from chemical and radiological/nuclear weapons. Other NIH Institutes and Centers will also contribute substantially to these efforts. 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.

Perhaps the most tangible signs of NIAID's biodefense research progress are the biocontainment research facilities now under construction, which will be capable of safely containing dangerous pathogens, enabling scientists to study such agents. 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 thirteen Regional Biocontainment Laboratories nationwide. In addition, three intramural biocontainment labs—on the NIH campus, on the National Interagency Biodefense Campus at Fort Detrick in Fredrick, MD, and at the NIAID Rocky Mountain Laboratories in Hamilton, MT—are either complete or under

construction. NIAID also has established a nationwide network of Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases Research; two new RCE awards were announced on June 1, 2005, bringing the total number of RCEs nationwide to ten.

The investment in biodefense research has already yielded substantial dividends, some of which are of immediate benefit while others provide considerable promise for the future. Our basic research and clinical trials have already greatly increased our ability to respond to the threats of smallpox, anthrax, and Ebola with new and improved vaccines. For example, in November 2004, DHHS awarded a contract for the acquisition of 75 million doses of a new anthrax vaccine to be held in the Strategic National Stockpile. NIAID's support of the development of this vaccine was instrumental in making this initiative possible. In addition, NIAID-supported scientists recently discovered that a poxvirus infection may be halted by a cancer drug aimed not at the virus, but at the host cellular machinery that the virus needs to spread from cell to cell. Although much work remains, this research provides a lead to not only a new therapeutic approach to poxviruses such as smallpox, but also a means of circumventing antiviral drug resistance for other viruses. In another example of critical new discoveries, NIAID-supported scientists demonstrated that host cell proteins called cathepsins play an essential role in the Ebola virus' ability to enter and infect cells, and that inhibitors of cathepsin activity block viral entry and reduce the production of infectious Ebola viruses. This suggests that drugs that inhibit the activity of cathepsins might be useful as anti-Ebola therapies.

NIAID's implementation of its Strategic Plan for Biodefense Research has been aided by the enactment of the Project BioShield Act of 2004. Project BioShield provides NIH additional flexibility in awarding contracts, cooperative agreements, and grants for research and development of critical medical countermeasures. The BioShield Act also provides NIH with streamlined personnel authority, which has allowed NIAID to hire highly-qualified individuals to fill key positions related to product development. Lastly, Project BioShield provides NIAID with additional authority for the construction of research facilities, which NIAID used to award grants in FY 2005 for the construction of four Regional Biocontainment Laboratories.

RESEARCH ON IMMUNE-MEDIATED DISEASES

Autoimmune diseases, allergic diseases, asthma and other immunologic diseases are significant causes of chronic disease and disability in the United States and throughout the world. Autoimmune diseases affect 5 to 8 percent of the U.S. population; asthma and allergic diseases together are the sixth leading cause of chronic disease and disability in this country; and asthma is the leading cause of hospitalizations and school absences among children. A promising strategy to treat and prevent immune-mediated diseases is known as immune tolerance. Immune tolerance therapies are designed to preprogram immune cells in a highly specific fashion to eliminate injurious immune responses, such as those seen in autoimmune diseases, while preserving protective responses needed to fight infection. The NIAID has established a comprehensive program in immune tolerance research, including basic research, preclinical testing of promising strategies in nonhuman primates, and clinical

evaluation through the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Western Europe, and Australia. Currently, NIAID is supporting more than 40 clinical trials of immune tolerance strategies to treat autoimmune diseases, allergic diseases, and transplant rejection.

NIAID-supported research in immune-mediated diseases has led to significant advances in our understanding of how to manage these diseases. For example, NIAID-supported scientists recently identified novel ways to non-invasively assess the risk of kidney graft rejection by using immunologic and genetic biomarkers present in urine. If validated in larger studies, these biomarkers would allow physicians a non-invasive way to monitor transplant recipients for organ rejection, and intervene before organ injury, a significant advance in the clinical management of transplant patients.

NIAID also remains committed to improving the health of children with asthma, particularly those who live in our Nation's inner cities. For example, NIAID-supported researchers recently published the results of a study on the effect of home-based interventions that reduce exposure to common allergens such as cockroaches, house dust mites, and tobacco smoke. The study found that the interventions resulted in 20 percent fewer days with asthma symptoms and 14 percent fewer unscheduled clinic visits through the intervention year. We anticipate that our extensive research portfolio will continue to illuminate the causes of asthma and other immune-mediated conditions, and lead to new interventions to reduce the burden of these serious diseases.

CONCLUSION

The research conducted at NIAID and at NIAID-sponsored laboratories encompasses a broad array of basic, applied and clinical studies. This research has resulted in tangible benefits to the American public and to individuals throughout the world. By supporting talented researchers and emphasizing a balance of basic studies and targeted research, we hope to continue to develop innovative technologies and treatments to combat a wide range of important diseases that afflict humanity.

ANTHONY S. FAUCI, M.D.

Director, National Institute of Allergy and Infectious Diseases
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Dr. Anthony S. Fauci, a native of Brooklyn, New York, received his M.D. degree from Cornell University Medical College in 1966. He then completed an internship and residency at The New York Hospital-Cornell Medical Center. In 1968, Dr. Fauci came to the National Institutes of Health (NIH) as a clinical associate in the Laboratory of Clinical Investigation (LCI) at the National Institute of Allergy and Infectious Diseases (NIAID). In 1974, he became Head of the Clinical Physiology Section, LCI, and in 1980 was appointed Chief of the Laboratory of Immunoregulation, a position he still holds. In 1984, Dr. Fauci became Director of NIAID, where he oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies. The NIAID budget for fiscal year 2006 is approximately $4.4 billion. Dr. Fauci serves as one of the key advisors to the White House and Department of Health and Human Services on global AIDS issues, and on initiatives to bolster medical and public health preparedness against emerging infectious disease threats such as pandemic influenza.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He has pioneered the field of human immunoregulation by making a number of basic scientific observations that serve as the basis for current understanding of the regulation of the human immune response. In addition, Dr. Fauci is widely recognized for delineating the precise mechanisms whereby immunosuppressive agents modulate the human immune response. He has developed effective therapies for formerly fatal diseases such as polyarteritis nodosa, Wegener's granulomatosis, and lymphomatoid granulomatosis. A 1985 Stanford University Arthritis Center Survey of the American Rheumatism Association membership ranked the work of Dr. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the previous 20 years.

Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body's defenses leading to its susceptibility to deadly infections. He also has delineated the mechanisms of induction of HIV expression by endogenous cytokines. Furthermore, he has been instrumental in developing strategies for the therapy and immune reconstitution of patients with this serious disease, as well as for a vaccine to prevent HIV infection. He continues to devote much of his research time to identifying the nature of the immunopathogenic mechanisms of HIV infection and the scope of the body's immune responses to the AIDS retrovirus.

In 2003, an Institute for Scientific Information study indicated that in the twenty year period from 1983 to 2002, Dr. Fauci was the 13th most-cited scientist among the 2.5 to 3 million authors in all disciplines throughout the world who published articles in scientific journals during that time frame. Dr. Fauci was the ninth most-cited scientist in the field of immunology in the period from January 1993 to June 30, 2003.

Through the years, Dr. Fauci has served as Visiting Professor at major medical centers throughout the country. He has delivered many major lectureships all over the world and is the recipient of numerous prestigious awards for his scientific accomplishments, including 30 honorary doctorate degrees from universities in the United States and abroad.

Dr. Fauci is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, the Institute of Medicine (Council Member), the American Philosophical Society, and the Royal Danish Academy of Science and Letters, as well as a number of other professional societies including the American College of Physicians, the American Society for Clinical Investigation, the Association of American Physicians, the Infectious Diseases Society of America, the American Association of Immunologists, and the American Academy of Allergy Asthma and Immunology. He serves on the editorial boards of many scientific journals; as an editor of Harrison's Principles of Internal Medicine; and as author, coauthor, or editor of more than 1,000 scientific publications, including several textbooks.

Department of Health and Human Services
Office of Budget
Richard J. Turman

Mr. Turman is the Deputy Assistant Secretary for Budget, HHS. He joined federal service as a Presidential Management Intern in 1987 at the Office of Management and Budget, where he worked as a Budget Examiner and later as a Branch Chief. He has worked as a Legislative Assistant in the Senate, as the Director of Federal Relations for an association of research universities, and as the Associate Director for Budget of the National Institutes of Health. He received a Bachelor's Degree from the University of California, Santa Cruz, and a Masters in Public Policy from the University of California, Berkeley.