

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

**FY 2008 Budget for the National Institutes of Health:
A New Vision for Medical Research (Part II)**

**Witness appearing before the
Senate Subcommittee on Labor-HHS-Education Appropriations**

**Anthony S. Fauci, M.D., Director
National Institute of Allergy and Infectious Diseases**

May 21, 2007

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) 2008 budget includes \$4,592,482,000.

The mission of NIAID is to conduct and support research to understand, treat, and prevent infectious and immune-mediated diseases. Infectious diseases include well-known killers such as HIV/AIDS, malaria, tuberculosis, lower respiratory infections and diarrheal illnesses; naturally emerging or re-emerging threats such as pandemic influenza and SARS; and “deliberately emerging” threats from potential agents of bioterrorism. Preemptive medicine, in the form of vaccines and other prevention tools, is a major focus of the NIAID research portfolio in infectious diseases. Immune-mediated disorders include autoimmune diseases such as type 1 diabetes, lupus, and rheumatoid arthritis as well as asthma, allergies, and problems associated with transplanted tissues and organs. Here again, preemptive medicine is an important component of our research efforts, as NIAID extramural scientists work to predict, prevent, and treat immune-mediated diseases more effectively.

The NIAID mission has two distinct mandates. First, NIAID must plan and execute a comprehensive, long-term program of basic and clinical research on well-recognized endemic infectious and immune-mediated diseases. Second—and in this case distinctive among the NIH Institutes—NIAID 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.

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 a classic example of a re-emerging disease. Because circulating human influenza viruses continually accumulate small changes, a new vaccine must be made for each influenza season. When an influenza virus emerges that has undergone a major genetic shift such that the global population has limited natural immunity but the virus can be easily transmitted among people, a worldwide pandemic can result. Three influenza pandemics occurred in the 20th century, including the 1918 pandemic that killed more than 50 million people worldwide.

It is imperative that we take a preemptive approach to the possibility that a new influenza virus will emerge to cause a 1918-like pandemic. How well we do that, however, depends to a large extent on improving how we cope with seasonal influenza, which kills an average of about 36,000 people in the United States each year. Control of both seasonal and pandemic influenza requires development of and access to a sufficient supply of effective vaccines and antiviral drugs, effective infection control measures, and clear public communication. In this regard, NIAID research has directly laid the foundation for improved influenza vaccine manufacturing methods, new

categories of vaccines that may work against multiple influenza strains, and the next generation of anti-influenza drugs. Certain of these goals will be accomplished through 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 goals will be accomplished through targeted projects, such as a program to screen compounds for antiviral activity against influenza viruses.

Since last year, we have made substantial progress in influenza vaccine research. The inactivated-virus H5N1 vaccine currently stockpiled by the Department of Health and Human Services has been shown in NIAID-sponsored clinical trials to be safe and capable of inducing an immune response predictive of being protective against the H5N1 virus in healthy adults, children, and seniors. Although the vaccine dose required to induce this response is high, studies on enhancing the immune response to lower doses by employing immune enhancers called adjuvants are showing promising preliminary results. NIAID also is collaborating with industry to pursue several other vaccine strategies in addition to inactivated virus H5N1 vaccines. For example, trials of cold-adapted, live-attenuated H5N1 vaccine candidates are underway, as is a Phase I clinical test of a novel DNA H5N1 vaccine candidate developed at the NIAID Vaccine Research Center.

We also have made progress in antiviral drug and diagnostic test research over the past year. An NIAID program that screens both licensed drugs and new drug candidates—first in cell culture systems and then in animal models—has identified several promising anti-influenza candidates that are now being further developed in partnership with industry sponsors. These include FluDase, which binds host cell receptors to prevent viral entry; T-705, which inhibits replication of viral RNA; and Peramavir, which inhibits an influenza enzyme called neuraminidase. Research into influenza diagnostics is being vigorously pursued. For example, NIAID-funded researchers, working in collaboration with scientists at the Centers for Disease Control and Prevention, have reported encouraging results with a potentially revolutionary diagnostic device called the MChip, which is capable of quickly and accurately identifying many influenza viruses, including H5N1.

Tuberculosis (TB) is another emerging threat, especially with regard to new and dangerous drug-resistant forms of *Mycobacterium tuberculosis* that are being seen with increasing frequency. About one-third of the global population is latently infected with the TB bacterium. WHO estimates that 8.9 million TB cases occurred in 2004, as did 1.7 million TB deaths; active TB is especially common among people with HIV. Currently, about 20% of new TB cases are a multi-drug resistant form (MDR-TB), meaning that they are resistant to two common and inexpensive antibiotics and are thus far more difficult to treat than uncomplicated TB cases. However, an even more resistant form, called extensively-drug resistant TB (XDR-TB), has appeared. XDR-TB already accounts for about 10% of all MDR-TB cases, that is, two percent of all new TB cases.

The emergence of XDR-TB was not unexpected, but was a predictable consequence of imperfect compliance with the long and complex regimens needed to treat TB. We have long supported a large portfolio of research to develop new drugs, vaccines, and diagnostics for TB and to evaluate improved treatment and prevention

regimens. As a result of that sustained effort, the “pipeline” of new countermeasures for TB is robust. At least nine new drugs are currently in clinical trials, including SQ-109, a promising candidate being developed in a private-public partnership with Sequella, Inc. After a hiatus of 60 years in which no new TB vaccines were clinically tested, nine candidates are now in human trials, and at least ten more are in preclinical development. In addition, to ensure that the NIAID TB research program continues to contribute effectively to the global response to this increasing threat, the Institute has developed a comprehensive strategic plan for MDR/XDR-TB that will help guide our research efforts. .

Influenza and TB are just two of many emerging and re-emerging infections on which NIAID conducts research. Malaria, long a leading cause of death worldwide, has become even more problematic because of the emergence of drug-resistant malaria parasites and insecticide-resistant mosquito vectors. NIAID supports a large portfolio of malaria research that has generated many promising drug and vaccine candidates, some of which are now in clinical trials; this research is related to the President’s Malaria Initiative, which was discussed at the December 2006 White House Malaria Summit. In addition, NIAID conducts research on many other less common, but nonetheless important tropical diseases such as leishmaniasis, trypanosomiasis, hookworm, and lymphatic filariasis, which exact an enormous toll worldwide.

HIV/AIDS RESEARCH

In the almost 26 years since it was first recognized, the acquired immune deficiency syndrome (AIDS) has become a global catastrophe. An estimated 39.5 million people worldwide are infected with HIV, the virus that causes AIDS. In 2006 alone, an estimated 4.3 million people were newly infected with HIV, and 2.9 million died of AIDS.

Although the global HIV situation remains grim, our government’s investment in HIV research has generated many solid successes, and the healthy pipeline of new drugs, vaccines, and other prevention methods promises more successes in the future. Antiretroviral therapies made possible by NIAID-supported research have transformed HIV from an almost uniformly fatal infection into a manageable chronic condition. In this regard, a recent study concluded that since 1996 these antiretroviral medications have saved at least 3 million years of life in the United States alone. These life-saving therapies are now reaching the developing world: 1.6 million persons are now receiving antiretroviral therapy, more than half of them with support from the President’s Emergency Plan for AIDS Relief (PEPFAR). In addition to these accomplishments, several new generation antiviral drugs that target HIV in novel ways are in the final stages of development.

Prevention efforts continue to be a major component of NIAID’s HIV research program. We have improved our ability to prevent mother-to-child transmission. Research to develop topical microbicides capable of blocking HIV transmission during sexual contact is proceeding vigorously. And in December 2006, two NIAID-supported trials in Kenya and Uganda showed that medically supervised circumcision of adult males can significantly lower their risk of contracting HIV through heterosexual intercourse. The most powerful tool to prevent HIV infection would be a

safe and effective HIV vaccine. NIAID is currently supporting 20 clinical trials of HIV vaccine candidates. Seven of these have moved beyond initial Phase I safety and immunogenicity testing. For example, in January 2007, a Phase IIb “proof of concept” trial of a non-replicating adenovirus vector modified to contain three HIV genes opened in South Africa. A related trial of the same candidate is ongoing in volunteers from North America, South America, Australia, and the Caribbean in collaboration with Merck pharmaceutical company. The NIAID Vaccine Research Center has also developed an HIV vaccine candidate that is currently being tested in Phase II trials, with an international Phase IIb efficacy trial set to begin later in 2007. Because of the enormous need for human testing of HIV drug, vaccine, and other prevention strategies, we recently reorganized our HIV/AIDS clinical trials network to make our clinical research capacity more efficient so that we can continue to meet evolving global AIDS research challenges. Additionally, NIH will contribute \$300 million to the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria in FY 2008.

BIODEFENSE RESEARCH

The possibility that terrorists will use a biological agent to mount an attack is a serious threat to the citizens of our nation and the world. Research to preempt and mitigate this threat is a key focus of NIAID, and complements our role in meeting the challenges of naturally emerging and re-emerging infectious diseases. Our strategic planning for biodefense research includes three essential pillars: *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. These efforts enhance not only our preparedness for a bioterrorism attack, but for naturally occurring endemic and emerging infectious diseases as well.

NIAID has undertaken a substantial expansion of biocontainment research facilities, which will greatly enhance our ability to safely and efficiently conduct research on infectious 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. Three intramural biocontainment labs—on the NIH campus, on the National Interagency Biodefense Campus at Fort Detrick in Frederick, Maryland, and at the NIAID Rocky Mountain Laboratories in Hamilton, Montana—are either complete or well under construction. In addition to these facilities, NIAID has established a nationwide network of ten Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases Research, which conduct research and development activities and provide training for future biodefense researchers.

The Institute’s efforts have already yielded substantial dividends as described in our periodic progress reports, the latest of which was issued in January 2007. For example, new or improved vaccines and therapies against anthrax, smallpox and Ebola virus have shown great promise; among these is ST-246, a promising smallpox drug candidate that protects both rodents and nonhuman primates from lethal challenge.

NIAID also has been assigned the responsibility to coordinate research to develop countermeasures against a range of radiological and chemical threats. We have established eight Centers for Medical Countermeasures against Radiation and four Centers for Countermeasures against Chemical Threats; in addition, basic and applied research is moving rapidly. We continue to coordinate and collaborate on these important components of our national security with our sister Institutes at NIH as well as interagency partners, including the Department of Defense, Department of Energy, and Department of Homeland Security.

RESEARCH ON IMMUNE-MEDIATED DISEASES

Autoimmune diseases, allergic diseases, asthma and other immune-mediated diseases are significant causes of chronic disease and disability in the United States and throughout the world. NIAID-supported research in immune-mediated diseases has led to significant advances in our understanding of how to manage these diseases.

One promising strategy to treat and prevent immune-mediated diseases is the induction of immune tolerance. Immune tolerance therapies are designed to “reprogram” immune cells to eliminate injurious immune responses, such as those seen in autoimmune diseases, while preserving protective responses needed to fight infection. 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). In an important study of people with severe diabetes, the ITN has shown that the transplantation of pancreatic cells can improve blood sugar control, protect patients from severely low blood sugar, and, in a few cases, relieve patients of the need for insulin injections; unfortunately, insulin independence was not sustained in most subjects. Further research is underway to improve this promising procedure.

Last year, NIAID-supported scientists reported the identification of new ways to non-invasively assess the risk of kidney graft rejection by using gene-expression based biomarkers of immunologic activity present in urine. These investigators are now conducting a multi-center study to validate these approaches that potentially could allow physicians to predict, prevent, and treat kidney rejection more effectively.

NIAID remains committed to improving the health of children with asthma, particularly those who live in our Nation’s inner cities. The NIAID-supported Inner City Asthma Consortium (ICAC) has undertaken two important efforts in this area. The ICAC is conducting the Urban Environment and Childhood Asthma (URECA) Study. Five hundred and fifty inner-city children have been enrolled at birth and will be followed prospectively during childhood. The goals of the study are to identify the immunologic causes of the development of recurrent wheezing, a surrogate marker for asthma in children under three, and to monitor the development of food allergies in this patient population.

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 will continue to develop innovative interventions to prevent, diagnose, and treat the wide range of infectious and immune-mediated diseases that afflict humanity.

ANTHONY S. FAUCI, M.D.
Director, National Institute of Allergy and Infectious Diseases
National Institutes of Health

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. 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 world's 10th most-cited HIV/AIDS researcher in the period 1996-2006.

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 31 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 1,100 scientific publications, including several textbooks.