

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2006 Budget Request

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

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Mr. Chairman and Members of the Committee:

I am pleased to present the Fiscal Year (FY) 2006 President's budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The FY 2006 budget of \$4,459,395,000 includes an increase of \$56,554,000 over the FY 2005 enacted level of \$4,402,841,000, comparable for transfers proposed in the President's request.

NIAID conducts research to understand, treat, and prevent infectious and immune-related diseases. Infectious diseases include well-known killers such as tuberculosis and malaria, emerging or re-emerging threats such as HIV/AIDS, SARS, West Nile Virus and influenza, and "deliberately emerging" threats from potential agents of bioterrorism such as those that cause anthrax and smallpox. Examples of immune-related diseases include autoimmune disorders such as type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, transplantation-related illnesses, asthma, and allergies.

Historically, NIAID has accomplished its mission with a strong commitment to basic and targeted research in immunology, microbiology, and infectious disease. In the 57 years since NIAID was founded, this approach has led directly to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people worldwide. In recent years, however, the growing realization that the nation needs a stronger defense against both naturally and deliberately emerging infectious diseases has led NIAID to adopt a new research paradigm that accelerates the development of safe and effective medical countermeasures. To accomplish this, we

have sought creative ways to modify our traditional process of research and development to move potential products ahead more rapidly while continuing to preserve the excellence in basic research that is a hallmark of NIAID, and all of NIH. The result is that we now take a much more proactive role in collaborating with academia, industry and other partners to move promising concepts into advanced product development and clinical testing.

BIODEFENSE RESEARCH

In the wake of the 2001 terrorist attacks, NIAID substantially expanded and accelerated its biodefense research program. The FY 2006 President's budget request for NIAID includes \$1,664,505,000 for these biodefense research and development activities. The NIAID Strategic Plan for Biodefense Research provides a blueprint for the construction of three essential pillars of the NIAID biodefense research program: *infrastructure* needed to safely conduct research on dangerous pathogens (\$30,000,000 in FY 2006); *basic research* on microbes and host immune defenses that serves as the foundation for applied research (\$612,190,000 in FY 2006); and targeted, milestone-driven *research and development of medical countermeasures* to create the vaccines, therapeutics and diagnostics that we would need in the event of a bioterror attack (\$1,022,315,000 in FY 2006).

The investment Congress has made in the NIAID biodefense research program has already begun to return substantial dividends in all three of these aspects of biodefense research. Dramatic advances have been achieved in the development of medical countermeasures against an attack with biological agents, and, although there is much

more to be accomplished, we are in a far stronger position today than we were only a few years ago. In September 2001, we had 15.4 million doses of smallpox vaccine available; today, we have more than 300 million doses. A next-generation smallpox vaccine called modified vaccinia Ankara (MVA) is in clinical testing and other vaccine candidates are in pre-clinical development stages. A new oral form of the antiviral drug cidofovir is in advanced product development for use in the event of a smallpox attack, as well as to treat the rare but serious complications of the classic smallpox vaccine. For anthrax, NIAID has aggressively pursued development of a new vaccine called rPA; the Department of Health and Human Services (DHHS) has contracted with VaxGen, Inc. to purchase 75 million doses of rPA under the BioShield legislation passed last year. This vaccine is derived using molecular biological methodologies and is produced using modern vaccine manufacturing techniques and may require fewer doses than the currently licensed vaccine. New anthrax therapies that can neutralize the anthrax toxin, such as monoclonal and polyclonal antibodies, are being developed. Candidate antibody treatments for the toxin that causes botulism are in development, as is a new vaccine to prevent the disease. Finally, an Ebola recombinant DNA vaccine is in initial human clinical trials at the NIAID Vaccine Research Center.

With regard to research infrastructure, many integrated research facilities are under construction to safely contain and study pathogens, including several new biodefense laboratories that will be owned and operated by NIAID. In addition, sites have been selected for the construction of two National Biocontainment Laboratories (NBLs) and nine Regional Biocontainment Laboratories (RBLs) at major universities around the

United States. All of these research laboratories will provide the secure facilities needed to carry out the nation's expanded biodefense research program in settings that protect workers and the surrounding communities. NIAID also has funded eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). This nationwide network of multidisciplinary academic centers will conduct wide-ranging research to better understand infectious agents that could be used in bioterrorism, and will develop diagnostics, therapeutics and vaccines needed for biodefense against these agents. In 2005, NIAID will fund two additional RCEs and three to four additional RBLs. NIAID also has developed and expanded contracts to screen new drugs against bioterrorism threat agents, developed new animal models for bioterrorism threat agents, and established a biodefense reagent and specimen repository.

Advances in Medicine rest on a foundation of basic research into the fundamental properties and mechanisms of life. In biodefense, these basic studies include sequencing and understanding of microbial genomes (genomics) and their products (proteomics), deciphering how microbes cause disease (pathogenesis), and examining how the human immune system and pathogens interact (immunology). NIAID-funded basic researchers have made significant progress since 2001 in each of these areas. For example, researchers have now determined the genetic sequence of at least one strain of every pathogen identified as a potential bioterror threat, and NIAID has established the Pathogen Functional Genomics Resource Center to help researchers apply and analyze these new genome sequence data. In pathogenesis, NIH researchers recently

determined the three-dimensional structure of the anthrax toxin bound tightly to a target cell surface receptor. This finding has provided new leads for the development of novel antitoxins that could save lives late in the course of anthrax disease when large amounts of toxin are present and antibiotics alone are no longer sufficient to save the patient. Finally, basic molecular and cellular studies of the human innate immune system, which is comprised of broadly active "first responder" cells and other mechanisms that are the first line of defense against infection, have been moving forward rapidly. These advances suggest it may be possible to develop fast-acting countermeasures that boost innate immune responses to mitigate the effects of a broad spectrum of bioterror pathogens or toxins. Manipulation of the innate immune system also could lead to the development of powerful adjuvants that can be used to increase the effectiveness of vaccines.

The knowledge and products that will flow from the NIAID biodefense research program, including research results, intellectual capital, laboratory resources, and countermeasures in the form of diagnostics, therapeutics, and vaccines, will help us cope with naturally emerging, re-emerging, and deliberately released microbes alike. Recent experience tells us that knowledge developed to understand one pathogen invariably applies to others. For example, when HIV first emerged, antiviral drug development was in its infancy. Now, new technologies have led to the development of more than 20 antiretroviral drugs that can effectively suppress HIV replication and dramatically reduce AIDS morbidity and mortality. These same technologies, and the lessons learned about antiviral drug development, are being applied to the development

of new generations of drugs against many viruses, including influenza, SARS, smallpox, and Ebola. Even if we are never confronted with another bioterror attack, the biodefense research and preparations being carried out now will without question prove to be very valuable.

HIV/AIDS RESEARCH

Only a few statistics are needed to present a profoundly disturbing picture of the still-emerging HIV/AIDS pandemic. Approximately 40 million people worldwide are living with HIV/AIDS, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). Every year, more than 5 million people worldwide are newly infected with the virus—about 14,000 each day; more than 95 percent of these people live in low and middle income countries. In the United States, nearly one million people are living with HIV/AIDS, and approximately 40,000 new infections occur annually, according to the Centers for Disease Control and Prevention. The death toll continues to climb steadily; worldwide, more than 20 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 due to HIV/AIDS. As shocking as these numbers are, they do not adequately communicate the physical and emotional devastation to individuals, families, and communities coping with HIV/AIDS, nor do they capture the terrible impact of HIV/AIDS on the economies and security of nations, and indeed on entire regions.

Even as the burden of HIV/AIDS continues to grow, recent progress in research is providing reasons for optimism. For example, several new antiretroviral drugs recently have entered the market, all of which were built on NIAID-sponsored research and/or were tested in NIAID clinical trials networks; many other new anti-HIV drugs are in clinical trials. Other novel approaches to anti-HIV drugs are in the research “pipeline.” For example, NIAID scientists, in collaboration with extramural colleagues and with industry, recently conducted a clinical trial to test a product, anti-CCR5, that binds to a new therapeutic target, the HIV co-receptor, thus preventing HIV infection of host cells.

The development of a safe and effective HIV vaccine is one of NIAID’s highest priorities. The scientific barriers to the creation of such a vaccine are extraordinarily high, and better coordination, collaboration and transparency of research worldwide would help to overcome them. To facilitate such an approach, NIAID participated heavily in the creation of a new initiative called the Global HIV/AIDS Vaccine Enterprise, which was endorsed by President Bush and the other G8 countries at their June, 2004 Summit meeting in Sea Island, GA. The project creates a worldwide consortium of people and organizations with a stake in HIV vaccine research who agree to harmonize their individual HIV vaccine efforts by following a unified Strategic Plan for HIV vaccine development. This plan was published on a publicly-accessible website in February 2005.

Other measures to prevent HIV transmission also are being vigorously pursued. For example, when I testified here last year I discussed our efforts to develop topically

applied microbicides that women could use to protect themselves from HIV and other sexually transmitted pathogens. More than 50 candidate agents have shown activity against HIV and other sexually transmitted diseases in the laboratory, and several of these have been shown to be safe and effective in animal models. In February 2005, a large international study, sponsored by NIAID and involving more than 3,000 women at high risk of acquiring HIV in the United States and five African countries, opened for enrollment. If these microbicides are proven to be safe and effective, they likely will become a very important means of slowing the pace of the HIV/AIDS epidemic.

RESEARCH ON OTHER EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Infectious diseases do not remain static, but continually and dramatically change over time. New pathogens, such as the Severe Acute Respiratory Syndrome (SARS) coronavirus, can emerge suddenly and familiar ones, such as influenza virus and West Nile virus, can re-emerge with new properties or in unfamiliar settings. We must always be on guard for such changes and be prepared to react to them as quickly as possible.

SARS is a prototypical example of a newly-emerging infectious disease. When SARS first came to the world's attention in early 2003 as an unknown, highly lethal and transmissible disease, researchers and public health authorities the world over immediately began to collaborate to understand it. In short order, NIAID-supported researchers and others in Hong Kong showed that SARS was caused by a previously

unrecognized coronavirus, epidemiologists unraveled its modes of transmission, and public health authorities were able to contain the initial outbreak.

Since then, NIAID has continued to pursue several approaches to the development of SARS antiviral therapies. For example, NIAID screening contracts have supported the evaluation of more than 20,000 chemicals for anti-SARS coronavirus activity. More than 1,400 compounds with activity against SARS coronavirus have been identified, including alpha interferon, a drug already approved by the FDA for the treatment of hepatitis B and C infections.

NIAID scientists and grantees also are working on several approaches to a SARS vaccine, including one that entered human clinical testing in December 2004. It is truly remarkable that two years ago we were facing an unknown global health threat, and now we are already testing a promising vaccine that may help us to counter that threat should it re-emerge.

When West Nile virus (WNV) first appeared in the Western hemisphere in 1999, NIAID immediately increased its basic research on the virus and undertook the development of new vaccines and treatments for the disease. NIAID currently supports the development of three types of WNV vaccine—one of which has entered initial clinical testing—and is developing candidate WNV therapies. For example, in 2004, NIAID expanded an ongoing clinical study in human volunteers that is evaluating the

safety and efficacy of the administration of antibodies against the virus as a means of treating or preventing West Nile virus encephalitis.

Influenza is a classic example of a re-emerging disease. Because the influenza virus continually changes, the U.S. influenza vaccine supply must be renewed each year. Although the egg-based technology currently in use has served us reasonably well for more than 40 years, it has limitations in flexibility in that surges in the need for additional or new vaccines cannot be readily accommodated due to the advance time that is required to provide for the annual requirement for hundreds of millions of fertilized chicken eggs to manufacture the vaccine. In addition, there is the ever present risk of contamination and the vicissitudes of yield of virus from this technique. The serious vaccine shortage that occurred this flu season underscores 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 to improve the flexibility and speed with which vaccines can be made.

NIAID supports several research projects and other initiatives intended to foster the development of new influenza vaccines and manufacturing methods that are simpler and more reliable, yield products that work against multiple influenza strains, and provide greater protection. DHHS has requested \$120 million in FY 2006 to help shift vaccine manufacture toward new cell-culture technologies, new production technologies, as well as to provide for year-round availability of eggs to provide for a secure supply and surge capacity. In addition, a technique developed by NIAID-

supported scientists called reverse genetics allows scientists to manipulate the genomes of influenza viruses to make the process of development of seed viruses for vaccines faster and more predictable.

Although the impact of influenza in a normal epidemic year is substantial, influenza viruses from animals occasionally cross into humans and, if the virus then acquires the ability to be easily transmitted between people, can cause a much more serious influenza pandemic. NIAID conducts a great deal of research to understand the viral biology and epidemiology that underpinned past pandemics and funds surveillance activities in Asia to detect the emergence of influenza viruses with pandemic potential. In addition, the DHHS draft Pandemic Influenza Response and Preparedness Plan directs NIAID to help develop and produce an effective vaccine as rapidly as possible that could be used should a pandemic alert be declared.

In recent years, avian influenza virus strains that can infect humans have emerged; the most worrisome are known as H9N2 and H5N1. In 1999 and 2003, an H9N2 influenza strain caused illness in people in Hong Kong. The H5N1 “bird flu” influenza strain was first detected in 1997 and has spread widely among wild and domestic birds. This latter virus has infected at least 55 people and killed 42 since January 2004, and there has been at least one documented case of human-to-human transmission.

NIAID has taken several steps to develop vaccines against both of these potential pandemic strains. NIAID contracted with Chiron Corporation to produce

investigational batches of an inactivated H9N2 vaccine, which will be evaluated clinically by NIAID this year. For H5N1, Aventis-Pasteur, Inc. and Chiron are both producing investigational lots of inactivated H5N1 vaccine preparations; additionally, DHHS has contracted with Aventis to produce up to 2 million doses to be stockpiled for emergency use, if needed, to vaccinate health workers, researchers, and, if indicated, the public in affected areas. Development and evaluation of a combination antiviral regimen against these potential pandemic influenza strains are also now under way.

RESEARCH ON IMMUNE-MEDIATED DISEASES

Immune-mediated diseases, including autoimmune diseases, allergic diseases, and asthma are important health challenges in the United States and abroad. One of the most promising strategies for developing treatments for a wide variety of these disorders is known as immune tolerance, in which researchers hope to selectively turn off injurious immune responses while leaving intact the protective responses needed to fight infection. To foster this research, NIAID sponsors the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Western Europe, and Australia dedicated to the clinical evaluation of promising therapies that can induce immune tolerance. The ITN will be recompleted in FY 2006.

Reducing the growing burden of asthma among inner-city minority children is another NIAID priority. NIAID-supported investigators recently reported the largest

study of its kind, showing that an intervention to reduce exposure to indoor allergens and tobacco smoke substantially reduced asthma severity and healthcare utilization among inner-city children. In 2004, NIAID's Inner-City Asthma Consortium launched a large study to define and analyze immunological and environmental influences upon the development of childhood asthma in a cohort of urban children followed from birth.

In closing, Mr. Chairman, I would like to take a moment to remember John R. La Montagne, Ph.D., the former deputy director of NIAID, who died suddenly on November 2 while traveling to a meeting of the Pan American Health Organization in Mexico City. Human infrastructure, in the form of a highly trained and deeply committed work force, is a critical component of any kind of medical research. Throughout John's almost 30 years at NIAID, his leadership and dedication to improving global health, as well as his generosity, wit, even-handedness and kindness, made him a cornerstone of the human infrastructure at NIAID. Personally, he was a dear friend and one of the finest people I have ever known. He is sorely missed.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee might have.

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 and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, 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 possible future bioterrorist attacks.

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 28 honorary doctorate degrees from universities in the United States and abroad.

Dr. Fauci is a member of the National Academy of Sciences, the American Philosophical Society, the Institute of Medicine of the National Academy of Sciences (Council Member), the American Academy of Arts and Sciences, 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

William R. Beldon

Mr. Beldon is currently serving as Deputy Assistant Secretary, Budget in the Department of Health and Human Services. He has been a Division Director in the Budget Office for sixteen years, most recently as Director of the Division of Discretionary Programs. Mr. Beldon started in federal service as an auditor in the Health, Education and Welfare Financial Management Intern program. Over the course of more than 30 years in the Budget Office, Mr. Beldon has held Program Analyst, Branch Chief and Division Director positions. Mr. Beldon received a Bachelor's Degree in History and Political Science from Marshall University and attended the University of Pittsburgh where he studied Public Administration. He resides in Fort Washington, Maryland.