

Appropriations Subcommittee Statement on the Fiscal Year 2004 Budget

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April 8, 2003

Mr. Chairman and Members of the Committee, good morning. I am pleased to present the President's budget request for the National Institute of General Medical Sciences (NIGMS). The fiscal year (FY) 2004 budget includes \$1,923 million, an increase of \$76 million over the FY 2003 enacted level of \$1,847 million comparable for transfers proposed in the President's request.

The NIH budget request includes the performance information required by the Government Performance and Results Act of 1993. Prominent in this data is NIH's fourth annual performance report, which compared our FY 2002 results to our FY 2002 performance plan goals.

An Impressive Track Record

Since its creation more than 40 years ago, the National Institute of General Medical Sciences has built an impressive track record as a strategic investor in the future of basic biomedical research. Though not a household name, NIGMS is highly respected in the scientific community as an Institute that nurtures the nation's brightest minds in biomedicine. Through its forward-thinking funding programs, NIGMS supports thousands of scientists nationwide whose fundamental research is laying the foundation for promising new advances in disease diagnosis, treatment, and prevention.

Perhaps the most notable indicator of that track record is the number of NIGMS-supported scientists who have won Nobel Prizes—a remarkable 53 to date. In 2002, both the Nobel Prize in Physiology or Medicine and the Nobel Prize in Chemistry went to long-time NIGMS grantees, Dr. H. Robert Horvitz of the Massachusetts Institute of Technology and Dr. John B. Fenn of Virginia Commonwealth University, respectively. Dr. Horvitz's discovery of key genes controlling cell death shed new light on illnesses such as AIDS, Parkinson's disease, stroke, and cancer. And Dr. Fenn's refinement of a technique called mass spectrometry has made it possible to analyze large molecules in biological samples, an advance now widely used for blood testing.

Our Institute's leadership in supporting biomedical science was also recognized in 2002 with the prestigious Albert Lasker Award for Basic Medical Research. NIGMS grantees Dr. James E. Rothman of the Memorial Sloan-Kettering Cancer Center and Dr. Randy W. Schekman of the University of California, Berkeley, were honored for discovering the universal molecular machinery that drives "cellular trafficking." Their work helped explain

vital processes such as how insulin is released in pancreatic cells, how organs develop inside embryos, and how viruses infect their hosts.

Yet another acknowledgment of NIGMS' contributions to biomedical research came late last year when the journal *Science* declared the discovery of how small RNA molecules control the behavior of genes to be the top scientific achievement of 2002. Funded in large part by grants from NIGMS, this "Breakthrough of the Year" research shows promise as the basis for new therapies to treat cancer, AIDS, and other diseases.

As we look ahead to FY 2004 and beyond, NIGMS is poised to help make possible even more ground-breaking advances in biomedical science. I would like to share with you some of our strategies for accomplishing this important mission.

Unraveling the 3-D Structures of Proteins

Fifty years ago, Drs. James Watson and Francis Crick made their famous discovery of the double-helix structure of DNA. This year, scientists will reach another milestone: the completion of a highly accurate sequence representing the entire set of genetic instructions encoded in human DNA. As the Human Genome Project achieves this landmark goal, its promise to usher in a new era of molecular-based medicine will depend on another, equally important undertaking: discovering all the proteins our genes make and the functions these cellular "workhorses" play in health and disease.

Key to this ambitious effort is the unraveling of the complex, three-dimensional structures of proteins. Determining these structures can in turn reveal how proteins function and help scientists tailor the design of new drugs to treat diseases. NIGMS is the world's single largest supporter of research in structural genomics, a field dedicated to discovering the structures of proteins using sophisticated computer-based methods.

In FY 2000, NIGMS launched the Protein Structure Initiative (PSI), with the goal of determining 10,000 protein structures in 10 years. The nine pilot research centers we currently support have made significant progress in developing tools for the high-throughput determination of protein structures and have begun to yield some promising results, with potential applications in biomedicine and beyond.

In November 2002, for example, NIGMS-funded researchers at Argonne National Laboratory determined the structure of a protein knot—one of only a few such structures seen in nature, and the first found in a protein from the most ancient type of single-celled organism, an archaebacterium. The microbe that the newly discovered protein comes from is of interest to industry for its ability to break down waste products and produce methane gas.

NIGMS is considering additional activities to help the centers reach their full capability, including a materials storage bank and a database for protein production and crystallization experiments. The production phase of the PSI, during which researchers will be rapidly deriving protein structures, will begin in FY 2005.

Harnessing Math & Computers to Solve Biological Problems

In addition to leading the way in structural genomics, NIGMS is also at another forefront: a shift in biomedical science often called the "mathematization" of biology. This shift represents a broadening of biologists' research focus from studying how individual biological molecules behave to investigating how a large number of molecules interact with one another. In order to model and predict these complex interactions, biomedical scientists are increasingly partnering with quantitative scientists, including mathematicians, physicists, computer scientists, and engineers. Together, they are applying their combined expertise to solve particularly challenging problems in biomedicine, such as understanding embryonic development, metabolism, cell growth, and cell death.

To encourage more quantitative approaches in biological studies, NIGMS established Centers of Excellence in Complex Biomedical Systems Research. The first awards were for two center grants and seven planning grants to lay the groundwork for future centers, designed to foster a multidisciplinary research environment for developing innovative methods to solve biomedical problems. These centers will also lead the way in training the next generation of computational biologists.

A good example of this teamwork is the recent work by NIGMS-funded researchers who have produced the first comprehensive "script of life," describing the regulation of all the genes in yeast. Reporting in the journal *Science* in October 2002, Dr. Richard Young, a biologist at the Whitehead Institute for Biomedical Research, and Dr. David Gifford, a computer scientist at the Massachusetts Institute of Technology, detailed how they used advanced, high-throughput biological and computing technologies to do in weeks what would have taken years to achieve using traditional techniques.

The mathematization of biology and its importance in modeling complex biological systems were also major themes at our Institute's "Visions of the Future" meeting, held in September 2002. NIGMS invited visionary scientific leaders to identify the most important and emerging areas of biomedical research. A recurring topic of discussion was the need to develop mechanisms that encourage cooperative interactions among mathematicians, physicists, computer scientists, engineers, and biologists. Moreover, meeting participants

stressed the need for more rigorous quantitative training of undergraduate and graduate students who are pursuing research careers in the life sciences.

Such interaction and training were cited as keys to realizing some of science's grandest visions. These include the development of "virtual" models—of cells, tissues, disease states, and ultimately entire organisms—as well as new imaging tools and methods for making "molecular movies" of cellular machinery. Such technologies will help fill enormous gaps in our understanding of how molecules move in three dimensions and how they interact inside living cells in real time. Through its support of research and training in computational biology and other areas that cross traditional academic boundaries, NIGMS is uniquely positioned to help turn these visions into reality.

Guarding Against Infectious Diseases & Bioterrorism

As concern grows over bioterrorism and the emergence of new infectious diseases, NIGMS is designing an initiative to address this threat using computational approaches and mathematical modeling. Such models will help predict the spread of microbes, the rate of disease progression in individuals, the effectiveness of different treatment or prevention strategies, and the community response to new infectious diseases. These predictions will, in turn, provide policymakers with critical information that will help them respond quickly to the threat of a new disease or bioterrorism attack.

This new initiative follows on the footsteps of another successful NIGMS program—one dealing with the evolution of infectious diseases. Deadly viruses and bacteria can adapt to seemingly limitless environmental conditions by making rapid genetic changes, far outpacing our own ability to adapt. This microbial evolution renders previously effective drugs useless and creates a moving target for drug designers. However, by analyzing the evolution of infectious organisms, researchers now have a leg up on how to outwit potentially dangerous microbes.

One application of this area of study is antibiotic resistance, an increasing problem throughout the world. Recently, NIGMS-funded researcher Dr. Barry G. Hall of the University of Rochester developed a computer simulation of microbial evolution. Dr. Hall determined through experiment which bacterial genes are most susceptible to changes that cause resistance to commonly used antibiotics. Using this approach, pharmaceutical companies could create drugs for which bacteria have no evolutionary escape route.

NIGMS is also leading the way in supporting structural studies of infectious diseases. For example, the final piece of the anthrax puzzle—the structure of the third toxic protein responsible for the deadly effects of the anthrax bacterium—was discovered last year by Dr. Wei-Jen Tang of the University of Chicago. The toxin, edema factor, causes potentially

lethal swelling and fluid buildup in the body. By completing the detailed, three-dimensional structure of edema factor, Dr. Tang also found that the protein appears to be an ideal drug target, opening the door to a possible new compound to combat anthrax infection, as well as other bacterial diseases.

Basic Research: A Vital Return on Investment

In closing, it is worth noting that our leading efforts in structural genomics, computational biology, complex biological systems, and multidisciplinary collaboration give NIGMS a pivotal role to play in the trans-NIH "Roadmap" initiatives. Through its partnerships with other NIH institutes and centers, NIGMS will help forge new pathways to discovery and research teams of the future.

It is also important to emphasize that all of the scientific advances I have shared with you today resulted from investing in basic research on fundamental biological processes—the central mission of NIGMS. As administrators of federal research dollars, we are asked to show what we have done to ensure the best possible return on that investment, and to show how we plan to continue doing so in the future. I hope that the examples I have mentioned—from our Nobel Prize-winning achievements to our cutting-edge initiatives—illustrate the tremendous value of basic biomedical research to the strength of our scientific workforce, the security of our nation, and the health of our people.

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