

Appropriations Subcommittee Statement on the Fiscal Year 2006 Budget

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March 9, 2005

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 General Medical Sciences (NIGMS). The FY 2006 budget includes \$1,955,170,000, an increase of \$11,103,000 over the FY 2005 enacted level of \$1,944,067,000 comparable for transfers proposed in the President's request.

Understanding Disease Requires Understanding Normal Function

As we go about our daily lives, most of us probably forget about the biological processes that make our bodies work. Our cells are constantly making new components, dividing, moving, and even dying. Complex mechanisms underlie each of these processes and elaborate networks integrate them to promote normal, healthy function. If any of these processes break down, the result can be cancer, diabetes, Alzheimer's, or a host of other diseases.

To improve our understanding of basic biological processes, we need to employ a wide range of approaches. These include conducting basic research, developing new technologies, and training tomorrow's scientists. In essence, this is the core mission of NIGMS. For more than 40 years, the Institute has focused on deepening understanding of critical life processes and the molecular underpinnings of disease. In this way, NIGMS lays the foundation for advances in the diagnosis, treatment, and prevention of many different illnesses.

Paradigm-Shifting Ideas and Their Application

NIGMS has an impressive track record of investing in research with big payoffs. One indication of this success comes from the many prestigious awards our grantees receive for their research. In each of the last 8 years, at least one Nobel Prize has been given to an NIGMS grantee. This year continues the trend: The 2004 Nobel Prize in chemistry went to Irwin Rose, Ph.D., a biochemist at the University of California, Irvine, whose work has been supported by the Institute for several decades. He brings the number of NIGMS-supported Nobel laureates to 57.

Rose shared the prize for his studies on how cells control the breakdown of unneeded proteins. The mechanism for this controlled breakdown underlies many processes in health and disease and is now the focus of literally thousands of research studies. The

discoveries flowing from this basic research are increasingly being translated into new therapies. For example, Alfred Goldberg, Ph.D., an NIGMS grantee at Harvard Medical School in Boston, initiated research that led to a new drug called Velcade®. This drug is used to treat multiple myeloma, a deadly type of bone marrow cancer. Velcade® works by targeting the proteasome—the molecular machine that breaks down unneeded proteins that Rose and his coworkers discovered. Velcade® is likely to be the first of a number of drugs based on the discovery of this process that is so fundamental to much of cell biology.

The path to new approaches for promoting health and preventing and treating diseases has several key elements. These include creatively exploring a range of biological systems, developing tools for expanding knowledge, finding appropriate ways to integrate this knowledge into practical applications, and, of course, having a workforce of scientists who have the motivation and the knowledge to drive these advances.

From Carnivorous Snails to a Novel Pain Treatment

It is tough to make a living as a carnivorous snail. A large family of such creatures, called cone snails, relies on extremely potent venom to paralyze prey almost instantly. Baldomero Olivera, Ph.D., a biologist at the University of Utah in Salt Lake City, has been studying cone snails for more than 25 years with NIGMS support, carefully separating the venom into its components and studying each one.

Remarkably, the venom components are small proteins that target structures within the neuromuscular system with exquisite specificity. Because of the roles of their targets and this great specificity, these proteins are powerful research tools and show great promise as drugs. The first drug to result from this work, Prialt®, was approved by the FDA in December 2004 to treat the chronic, intractable pain often endured by people with cancer, AIDS, or certain neurological disorders. One thousand times more powerful than morphine, this new pain medication is thought to be non-addictive.

Other recently discovered pathways are leading to new drugs as well. The process of RNA interference, first characterized in roundworms by NIGMS grantees, can specifically silence individual targeted genes. Harnessing this process has allowed scientists to precisely control genes, leading to exciting new research tools and promising new ways to treat diseases including HIV, hepatitis, and cardiovascular disease. An RNA interference-based drug to treat the blinding eye disease of macular degeneration is currently in clinical trials.

The Shapes of Things to Come

The human genome is expressed primarily through proteins, the molecules that perform virtually all of the body's activities. Based on their amino acid sequences, proteins fold into complex shapes that determine their functions, including which other molecules they bind

to form complex assemblies. Powerful techniques have been developed for determining protein structures in great detail. Thousands of such structures have been determined, providing deep insights into how biological systems function in health and disease and driving the development of new drugs and other therapies. Much of this work has been performed by individual investigators working on individual proteins chosen based on their biological context. A productive laboratory might determine two to four structures per year. This approach continues to be effective, but it is too slow to keep up with the vast number of potential protein targets now accessible through genomic studies.

To complement the contributions of individual investigators, NIGMS launched the Protein Structure Initiative (PSI) in 2000 with the goal of developing technologies and processes to enable researchers to quickly, cheaply, and reliably determine the three-dimensional structures of proteins. After 4 years, the nine PSI pilot centers can produce several structures each week, and the total number of structures solved by the PSI centers has now passed the milestone of 1,000!

With the second phase of the initiative beginning this summer, the PSI will use the tools and methods developed in the pilot phase to continue technology development and to determine more protein structures, including some that were too complex to tackle during the pilot phase. Researchers will use these structures to determine and understand protein function, predict the structures of other proteins, identify targets for drug development, design molecules to fit those targets, and compare proteins from normal and diseased tissues.

An important activity related to the PSI is the structural biology component of the NIH Roadmap for Medical Research, which funded two Centers for Innovation in Membrane Protein Production to aid structural studies of this major class of proteins. Difficulties inherent in studying membrane proteins mean that we know relatively little about them, despite the fact that they represent up to a third of all proteins and are the targets for a large number of therapeutic drugs. NIGMS is actively involved in other Roadmap initiatives, as well, including those in the areas of high-risk research (specifically, the NIH Director's Pioneer Award), bioinformatics and computational biology, molecular libraries and imaging, and interdisciplinary research.

Computers Model Complex Systems

Today's biomedical research has moved beyond describing the parts of living systems to focusing on the complex, dynamic interactions of those parts. One of the best ways to approach this formidable challenge is to use computers to model and manipulate the systems.

Among the places this is happening are the five NIGMS Systems Biology Centers. Multidisciplinary teams of researchers at these centers are addressing such fundamental questions as how cells divide, differentiate, and communicate and how different kinds of environmental stress affect cell and tissue function.

At the other end of the spectrum, NIGMS-supported researchers are investigating how human systems contribute to the spread of infectious diseases. The researchers, part of the Institute's Models of Infectious Disease Agent Study (MIDAS) initiative, use computational approaches to simulate disease outbreaks, whether they occur naturally or result from bioterrorism. In much the same way as weather forecasters use computer models to predict the landfall of hurricanes, scientists can use the MIDAS models to make predictions about potential epidemics. These models will assist policymakers, public health workers, and other researchers in understanding and responding to new infectious disease outbreaks.

Responding to the medical community's growing concern that avian influenza could cause the next flu pandemic, the MIDAS network currently is simulating the outbreak of a deadly bird flu strain in a hypothetical human community. The computer models incorporate data on population density and age structure, distribution of schools, locations of hospitals and clinics, travel, and the infectiousness of the virus. The models will predict the effects of different strategies to contain the spread of infection, such as vaccinating specific groups of people or restricting travel. Preliminary results from the avian flu modeling project should be available by mid-2005.

Diversity Drives Discovery

To continue making rapid progress in biomedical research and improving human health, we need to ensure that the pool of biomedical scientists reflects the great diversity of our nation. This diversity can spark new research questions and offer different approaches to answering them. NIGMS promotes this diversity in a number of ways.

Through our Division of Minority Opportunities in Research, we offer programs that encourage and prepare underrepresented minority students for research careers. Other programs enhance science curricula and faculty research capabilities at institutions with substantial minority enrollments.

We require our institutional training programs to recruit and retain underrepresented minority students, as well. And we promote diversity of ideas through interdisciplinary training programs and through efforts to bring the expertise of researchers in a variety of fields, from the physical to the behavioral sciences, to bear on biomedical questions. One

example is our partnership with the National Science Foundation that supports more than 30 research grants at the interface of biology and mathematics.

Expanding the Horizon

Our increasing knowledge of the biological processes that underpin health and disease holds great promise for new drugs and better diagnostic techniques in the future. A more complete picture of how these processes work—and don't work—may lead to new methods for preventing illness altogether.

At the same time, it is important to remember that breakthroughs are often based on years of scientific research, with each new result building on many previous ones. Each discovery pushes back the frontier and reveals intriguing new questions and avenues for future study. While we can't always predict what we'll find, we can guarantee that the journey will bring us closer to our goal of understanding human health and disease.

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