

Appropriations Subcommittee Statement on the Fiscal Year 2005 Budget

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April 1, 2004 and April 22, 2004

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) 2005 budget includes a sum of approximately \$1,960 million which reflects an increase of \$55 million over the FY 2004 enacted level of \$1,905 million.

Cross-Cutting and Cutting-Edge Research

Both before joining NIGMS as its new director last November and since then, I have been tremendously impressed by the Institute's leadership in supporting basic biomedical research—that is, scientific studies into the most fundamental biological processes that govern human health. The kinds of research that we fund are both cross-cutting and cutting-edge. NIGMS-supported studies have shed light on everything from the three-dimensional structures of individual proteins—life's building blocks—to the complex interactions between molecules inside cells. More importantly, by uncovering the previously hidden workings of this cellular machinery, not only do we gain a better understanding of the very basis of human health, but we also gain valuable clues to fixing this machinery when it goes awry. Those clues are essential in helping scientists develop better methods to diagnose, treat, and even prevent a wide range of human diseases.

NIGMS has a successful track record of supporting the nation's brightest minds in basic biomedical science. Perhaps the highest recognition of that success can be seen in the number of Nobel Prizes that NIGMS grantees have won over the past four decades: a remarkable 55 to date. This past year was no exception. Roderick MacKinnon, M.D., a biophysicist at the Rockefeller University and a long-time NIGMS grantee, won the 2003 Nobel Prize in chemistry for discovering the structure and function of membrane ion channels—the "gatekeepers" that control what essential molecules move in and out of cells. MacKinnon's breakthrough provides direct visualization of the basis for the electric circuits that are responsible for the functioning of our brains and the beating of our hearts. The detailed structural information is revealing how local anesthetics work and why some drugs have life-threatening cardiac side effects. The work of literally thousands of other researchers has been redirected in response to his discoveries.

NIGMS' impressive return on investment in basic biomedical research is also evidenced by the many other prestigious awards honoring our grantees. In 2003, Rockefeller researcher C. David Allis, Ph.D., won the third annual Wiley Prize in the Biomedical Sciences for his work on chromatin, the complex of DNA with proteins that packages genetic information

inside each cell nucleus. The structure of chromatin is largely responsible for why one cell is a nerve cell while another cell is a muscle cell, even though they contain exactly the same DNA sequence. Allis' studies of the chemical modifications that regulate chromatin hold promise for learning how to control genes that suppress and inhibit the growth of tumors in cancer. The previous year, two other NIGMS grantees—Andrew Z. Fire, Ph.D., of the Stanford University School of Medicine, and Craig C. Mello, Ph.D., of the University of Massachusetts Medical School—were among the winners of the second annual Wiley Prize for their groundbreaking discovery of gene silencing by a mechanism called RNA interference. The phenomenon of RNA interference is the subject of upcoming meetings at both the National Academy of Sciences and NIH because of its potential impact for both basic research and for entirely novel approaches to preventing and treating disease.

Even greater advances in biomedical science are possible in the years to come. Through forward-thinking programs designed to foster innovative research and train the next generation of pioneering scientists, NIGMS is playing a leading role in the NIH Roadmap for Medical Research—the exciting new vision of the future recently launched by NIH director Elias Zerhouni, M.D. I would like to share with you some of the key strategies we have developed to help realize this important vision.

Blazing a Trail for the NIH Roadmap

Throughout its history, NIGMS has helped push back the frontiers of medical knowledge primarily by funding the most promising research grant applications submitted by both new and established scientists. This so-called investigator-initiated research—supported through the NIH's R01 grant mechanism—continues to be the most important instrument NIGMS has to promote experimentally based, hypothesis-driven research—the heart of our nation's scientific mission.

In recent years, NIGMS launched a number of larger, targeted initiatives to address both significant opportunities and critical gaps in biomedical research today. In many ways, programs such as NIGMS' Protein Structure Initiative (PSI), its large-scale collaborative "glue grants," and its new Center for Bioinformatics and Computational Biology have blazed a trail for the NIH Roadmap. Today, NIGMS is well positioned to participate with other NIH institutes in transforming the nation's biomedical research capabilities and accelerating the translation of scientific discoveries from the bench to the bedside.

Structural biology is part of the Roadmap's New Pathways to Discovery theme, and NIGMS is playing a key role in this area. One major activity is the PSI, an ambitious 10-year project launched in 2000. The aim of the PSI is to solve the three-dimensional structures of thousands of proteins experimentally and ultimately produce computer-based tools for

modeling the 3-D structure of any protein from its genetic spelling, or sequence. Knowing the structures of proteins helps scientists understand how these molecules function in health and disease and aids in the development of new medicines.

Results from the nine pilot centers set up in the first phase of the PSI are promising, demonstrating that automated protein production "factories" are feasible and are yielding high-resolution data that is already being used by scientists around the world. This year, NIGMS plans to ramp up the PSI in its second phase, with the funding of large-scale centers that will dramatically reduce the time and cost of solving protein structures, as well as specialized centers that will tackle challenging problems such as membrane proteins and protein complexes.

NIGMS is also contributing substantially to Roadmap-related initiatives through its support of research aimed at unraveling the complexities of living systems. In 2003, the Institute awarded its fifth glue grant, bringing together a diverse team of scientists to assemble a complete picture of lipids—fats and oils—inside cells, and the role they play in heart disease, arthritis, and other major illnesses. Other ongoing glue grants awarded since the program started in 2000 include projects aimed at understanding cellular signaling and communication, cell movement, and inflammation and the way the body responds to injury.

Last year, NIGMS also added two new Centers of Excellence in Complex Biomedical Systems Research. At these centers, interdisciplinary teams of researchers from both the biological and physical sciences will focus on the emerging field of "systems biology," which seeks to find hidden patterns of biological interactions at all levels, from individual proteins to entire organisms. The new centers join two others launched the previous year with NIGMS funding.

Computer-Based Solutions to Biomedical Challenges

Harnessing the power of computers to solve complex problems in biology is another major theme in both the NIH Roadmap and NIGMS' research mission. In 2003, the Institute's recently created Center for Bioinformatics and Computational Biology welcomed its first director, Eric Jakobsson, Ph.D., a leading researcher in the field from the University of Illinois at Urbana-Champaign. Dr. Jakobsson has been instrumental in launching one of the first Roadmap initiatives, a program to fund the creation of NIH National Centers for Biomedical Computing. The centers will bring together computer scientists, biomedical researchers, and experts from the experimental, clinical, and behavioral sciences to tackle such challenges as developing computer simulations that will accurately model the complex inner workings of the human brain and other vital systems.

One of the most exciting prospects for computational biology is the promise of turning the vast amounts of data generated by the Human Genome Project into promising new medical treatments that are tailored to the individual. As Allen D. Roses, M.D., senior vice-president of genetics research at GlaxoSmithKline, recently observed, "The vast majority of drugs—more than 90 percent—only work in 30 to 50 percent of the people." NIGMS is addressing this critical issue through the Pharmacogenetics Research Network, a nationwide collaboration of scientists from academia, government, and industry that the Institute spearheaded in 2000, with additional funding from five other NIH institutes. The network has already produced a key computer-based resource that scientists are now actively using: the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB). With this and other tools at their disposal, scientists will be able to study the effect of genes on people's responses to a wide variety of medicines including antidepressants, chemotherapy, drugs for asthma and heart disease, and many others. The ultimate goal of pharmacogenetics research is to help tailor medicines to people's unique genetic make-ups, thus making medicines safer and more effective for everyone.

Computational biology is also at the heart of another NIGMS initiative: the Models of Infectious Disease Agent Study (MIDAS). An integral component of the overall NIH biodefense plan, MIDAS is a network of scientists who will produce user-friendly computational models for policymakers, public health workers, and other researchers to assist them in making better-informed decisions about emerging infectious diseases. The first centers funded through the MIDAS initiative will launch this year and are expected to contribute significantly to our ability to prevent, detect, and respond to new infectious diseases, either natural or human-made.

Other NIH Roadmap-related initiatives include NIGMS' program to establish high-quality chemical libraries that provide scientists with powerful tools for discovering potential new drugs, and a portfolio of grants designed to stimulate the development of new molecular imaging technologies that can be harnessed to visualize the actions of individual molecules over time in living cells. The effort to create, distribute, and apply these tools will be tremendously enhanced by initiatives that are part of the Roadmap.

Team Science and Interdisciplinary Training

The increasingly complex nature of biomedical research today demands new approaches to carrying out the scientific enterprise. NIGMS has been at the forefront of addressing this issue, especially in its support for "team science"—interdisciplinary research that seeks to combine the skills and expertise of scientists from diverse fields and backgrounds. And now as part of another major theme in the NIH Roadmap—Research Teams of the Future—NIGMS is bringing its own experience to the table to help build successful synergies in

large-scale research collaborations, and to help prepare the next generation of biomedical scientists trained in multiple disciplines.

For example, NIGMS has led the way in supporting cross-disciplinary research and training through its Medical Scientist Training Program—which leads to the combined M.D.-Ph.D. degree and produces investigators who can bridge the gap between basic and clinical research. Other NIGMS programs support training in the cellular, biochemical, and molecular sciences; systems and integrative biology; the pharmacological sciences; genetics; molecular biophysics; biotechnology; the chemistry-biology interface; and bioinformatics and computational biology.

Many NIGMS research and training programs combine both the biological sciences—cellular and molecular biology, genetics—and the quantitative sciences—physics, chemistry, engineering, mathematics. Indeed, bringing together these two scientific cultures is essential if we are to continue to make important advances in biomedical research in the 21st century. That growing realization has spurred a flurry of activity in recent years. For example, NIGMS joined forces with the National Science Foundation in 2002 to launch an initiative to encourage the use of mathematical tools and approaches to study biology. NIGMS is also partnering with the NIH Office of Science Education on a program to transform undergraduate biology education by incorporating examples and perspectives from the quantitative sciences into biology courses. This program responds to the National Research Council's Bio2010 report.

NIGMS also has a long-standing commitment to increasing the number of underrepresented minorities engaged in biomedical research. Through our Division of Minority Opportunities in Research, NIGMS takes a leading role at NIH to encourage and prepare minority students to pursue training for scientific careers and to enhance the science curricula and faculty research capabilities at institutions with substantial minority enrollments. Both these programs and the efforts to train and recruit more scientists from the physical sciences into biomedical research are essential if we are going to have the biomedical workforce necessary to solve the challenging problems that lead to human disease and drive up the costs of providing health care.

Balancing Large- and Small-Scale Science

As promising and worthwhile as these major initiatives are, we must not lose sight of NIGMS' mainstay over the past four decades: investigator-initiated research. By encouraging the best and brightest basic scientists to pursue new directions in their fields, NIGMS has made tremendous contributions to advancing biomedical science. It is often a single investigator, supported by a single grant, who discovers something that turns out to

be the tip of a very important iceberg. And we must continue to support these creative minds in order to sow the seeds for tomorrow's advances.

At the same time, we must recognize the need to invest strategically in targeted, larger-scale research to meet the critical needs of ensuring the nation's health and well-being, its technological competence and competitiveness, and its security. In short, we need to balance small- and large-scale science in a way that both catalyzes and capitalizes on innovation. With our experience in managing thousands of individual research grants every year along with a growing number of multi-institutional, multidisciplinary research efforts, NIGMS can strike that balance while leaving open the door to future directions that are still beyond our powers of prediction.

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