

Appropriations Subcommittee Statement on the Fiscal Year 2003 Budget

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March 13, 2002

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) for FY 2003, a sum of \$1,881,378,000, which reflects an increase of \$154,911,000 over the comparable Fiscal Year 2002 appropriation.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's third annual performance report, which compared our FY 2001 results to the goals in our FY 2001 performance plan.

Today, 40 years since NIGMS was established, we can look back and reflect on the many accomplishments of the Institute. NIGMS-funded research has played a major role in building a strong foundation for all of biomedicine, producing a steady stream of research advances in a spectrum of disciplines. These advances have emerged from fundamental research in very basic areas like genetics, chemistry, and cell biology; and from more applied areas of science such as the body's response to medicines and to injury caused by trauma or burns.

A Good Model

In our anniversary year, I think it is fitting to showcase some of the medical benefits that have grown out of NIGMS's strong investment in supporting basic research--especially that obtained from studies with non-mammalian model organisms. Years of basic research with model organisms continue to yield valuable information, including important medical insights. An explosion of new discoveries rooted in basic investigations of the biology of the common baker's yeast are paving the way for effective means to treat infections caused by microbial cousins of this common fungus, including the potentially dangerous yeast *C. albicans*. This species of yeast causes vaginal and gut infections and can cause life-threatening problems for people with weakened immune systems, such as AIDS patients or transplant recipients.

Other recent medical advances stemming from studies with yeast include several important research findings on biofilms, specialized "mats" of bacteria or fungi that tend to be particularly resistant to medical attack. Biofilms, which account for everything from dental plaque to unsightly toilet bowl stains, also thrive in the clogged airways of people with cystic fibrosis, where they create tremendous problems. NIGMS-funded research with

baker's yeast has shown that these ordinary fungi can be made to form a biofilm structure, providing scientists with a robust, inexpensive, and safe system to study the properties of biofilms as well as test drugs to block the formation of biofilms.

There is no question that, for years to come, scientists will continue to relish the versatility and economy of baker's yeast, properties that make this model organism an extraordinarily resilient and productive research tool.

I would like to move on to an exciting story about a team of scientists who are getting some old drugs to try new tricks. Over time, the group's research findings on the chemical and physical properties of certain enzymes and other proteins involved in basic metabolism led to the idea that a certain class of chemicals may live a dual life. These so-called "bisphosphonates," the researchers discovered, are capable of blocking an enzyme critical to the livelihood of parasites, the organisms that cause malaria and other infectious scourges. But the same chemicals can also knock out a human enzyme whose activity breaks down bone during osteoporosis. This multifaceted group of researchers put their heads together and--blending chemistry, biology, and very fast computers--discovered that a key step in parasite metabolism could indeed be knocked out by the anti-osteoporosis medicines Fosamax®, Actonel®, and Aredia®. Their new research shows that fairly low concentrations of these FDA-approved drugs can do away with parasites while sparing human cells. The scientists are now testing the drugs in animal models of the diseases and so far have obtained cures--in mice--of certain types of leishmaniasis, another disease caused by parasites. If the medicines work well in animal models, testing the drugs in people could occur relatively quickly, since the medicines have already been approved for other uses, and therefore have already been tested for safety in people.

Other fundamental lines of inquiry have led to unexpected practical benefits in treating disease. Ten years of intense analysis of the properties and functions of a plant enzyme led to the discovery that the active ingredient in the weedkiller Roundup® attacks this particular enzyme. The enzyme, the researchers learned years later, also happens to be present in parasites, fungi, and other microorganisms. From this discovery, the potential medicinal value of interfering with this enzyme came into clear view. Fundamental biophysical studies that show what this enzyme looks like up close have now handed scientists a blueprint for designing chemical compounds to disable the action of this critical molecule. This research will likely lead to potent new medicines to treat parasites, bacteria, and fungi that cause illness in people.

Medicines from Land and Sea

NIGMS's research investment in chemistry has yielded important medical treatments from the ocean, which can be illustrated by two examples. The first is a poison derived from the venom of a marine snail species called *Conus*. To marine predators, a small molecule produced by *Conus* snails is deadly and serves as a form of defense. But for people with certain forms of chronic pain, this molecule may be extremely helpful in numbing pain that is unresponsive to other methods of pain treatment. Nearly a decade of NIGMS research probing the properties and physiological effects of *Conus* poisons has matured into the discovery and production of the compound Ziconotide. This medicine has completed clinical testing and is awaiting FDA approval. If approved, Ziconotide will be the first marine organism-based pharmaceutical product. Due to the fact that so many *Conus* varieties exist in nature, and that each snail produces many different venoms, the pharmaceutical potential of this humble organism seems vast. Indeed, a number of other promising *Conus*-derived molecules are in the drug development pipeline for a range of clinical applications, including treatment for burn pain, eye pain, postoperative surgical pain, and certain nervous system disorders.

A second example of medicine from the sea is a chemical called "Et743," which was originally discovered in a Caribbean sea squirt called *Ecteinascidia turbinata*. Scientists have shown that Et743 is an extremely powerful killer of cancer cells, particularly soft-tissue sarcomas, and the drug is now in late-stage clinical testing. Despite the medical potential of Et743, a severe shortcoming early on was its very limited availability in nature. NIGMS-funded chemists made an important step in extending the utility of this chemical by figuring out how to make it easily in the lab, starting with simple materials.

Getting back to land, I want to highlight some medical benefits offered through research with a terrestrial laboratory darling, the ordinary fruit fly. Fundamental research using these tiny red-eyed insects has shed light on many basic features of the development of all of the body parts of embryos, including the development of human embryos. NIGMS-supported scientists discovered a fruit fly gene whose protein product helps fly ovary cells move to where they need to go during the normal process of development of the ovaries. This fly gene is strikingly similar to a human gene that, when misspelled, is overproduced in human breast and ovarian cancers. The work not only adds to fundamental knowledge about how cells know where to go as they meld together into organs and tissues, but it also provides a useful tool for cancer researchers studying the causes and treatments for breast and ovarian cancer.

Recently, NIGMS-funded genetic research with fruit flies demonstrated that these insects may hold a key to curing a host of different human diseases. One study unearthed 548 fly genes that are so similar to genes involved in 714 different human genetic disorders that

the likelihood of the similarity occurring by chance alone is 1 in 10 billion. What this means is that scientists can look for causes and treatments for blindness, cancer, Parkinson's disease, diabetes, and many other disorders using lab fruit flies that are inexpensive and can be bred very quickly. Ultimately, scientists predict that fly genes will play an important role in the study of at least 1,000 of the 5,000 known genetic diseases in people.

Research Training

NIGMS is proud once again to cite the Nobel Prize-winning work of two of its long-time grantees. Geneticist Dr. Leland Hartwell and chemist Dr. Barry Sharpless each received the Nobel Prize in 2001 for their work on the cell cycle and chemical tools called chiral catalysts, respectively. Such quality scientific research gets done by quality researchers, and a vital component of the NIGMS mission is training the next generation of scientists. NIGMS maintains its leading role at NIH in research training by supporting nearly 44 percent of the predoctoral trainees and roughly 29 percent of all trainees receiving training funds from NIH. In recognition of the interdisciplinary nature of biomedical research today, all of NIGMS's training programs place a strong emphasis on crossing disciplinary boundaries. Nearly half of the NIGMS-funded biotechnology predoctoral fellowship programs, for instance, are centered in engineering departments.

In keeping with its commitment to training a diverse research work force, NIGMS is vigilant to how institutions recruit and retain trainees who are members of underrepresented minority populations. To propel these efforts, NIGMS sponsored a successful workshop in May 2001 at which institutions shared best practices for minority recruitment and retention in their training programs. We are promoting continued sharing via a minority recruitment and retention strategies Web site.

Looking more globally at our minority programs, I want to bring to your attention a few very interesting and fruitful examples of outreach with Native American populations. Together with National Human Genome Research Institute staff, this past year NIGMS staff organized a visit to Diné College on the Navajo Reservation. Staff of the NIGMS Division of Minority Opportunities in Research continue to work tirelessly to motivate, guide, and assist minority institutions, faculty members, and other prospective grantees who are new to the NIH funding system. I would like to highlight one particularly innovative ongoing partnership with the Indian Health Service. Beginning in FY 2001, NIGMS established a collaborative program designed to improve research and research training responsive to the needs of Native American communities. The Native American Research Centers for Health (NARCH) program supports partnerships between American Indian or Alaska Native tribes and research-intensive institutions.

Special Initiatives

Of course, a key component to providing top-notch training programs is to closely follow the directions in which science takes us, and NIGMS has listened carefully to what the scientific community has to say about what's needed to move science forward. To that end, I am happy to report that NIGMS-funded initiatives aiming to pull together science from different, complementary fields of study are moving ahead. Important progress is being made by researchers in the NIGMS-led NIH Pharmacogenetics Research Network, with four new research teams joining the existing effort in September 2001. Two new teams of scientists joined NIGMS's Protein Structure Initiative, and three multifaceted research groups were awarded large-scale "glue" grants to study how cells communicate via natural sugar molecules, how cells move around the body, and how the body responds to injury caused by trauma and burns.

Conclusion

NIGMS remains dedicated to developing and sustaining programs that ensure the advancement of the basic biomedical research that will fuel the discovery of tomorrow's medicines.

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