DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

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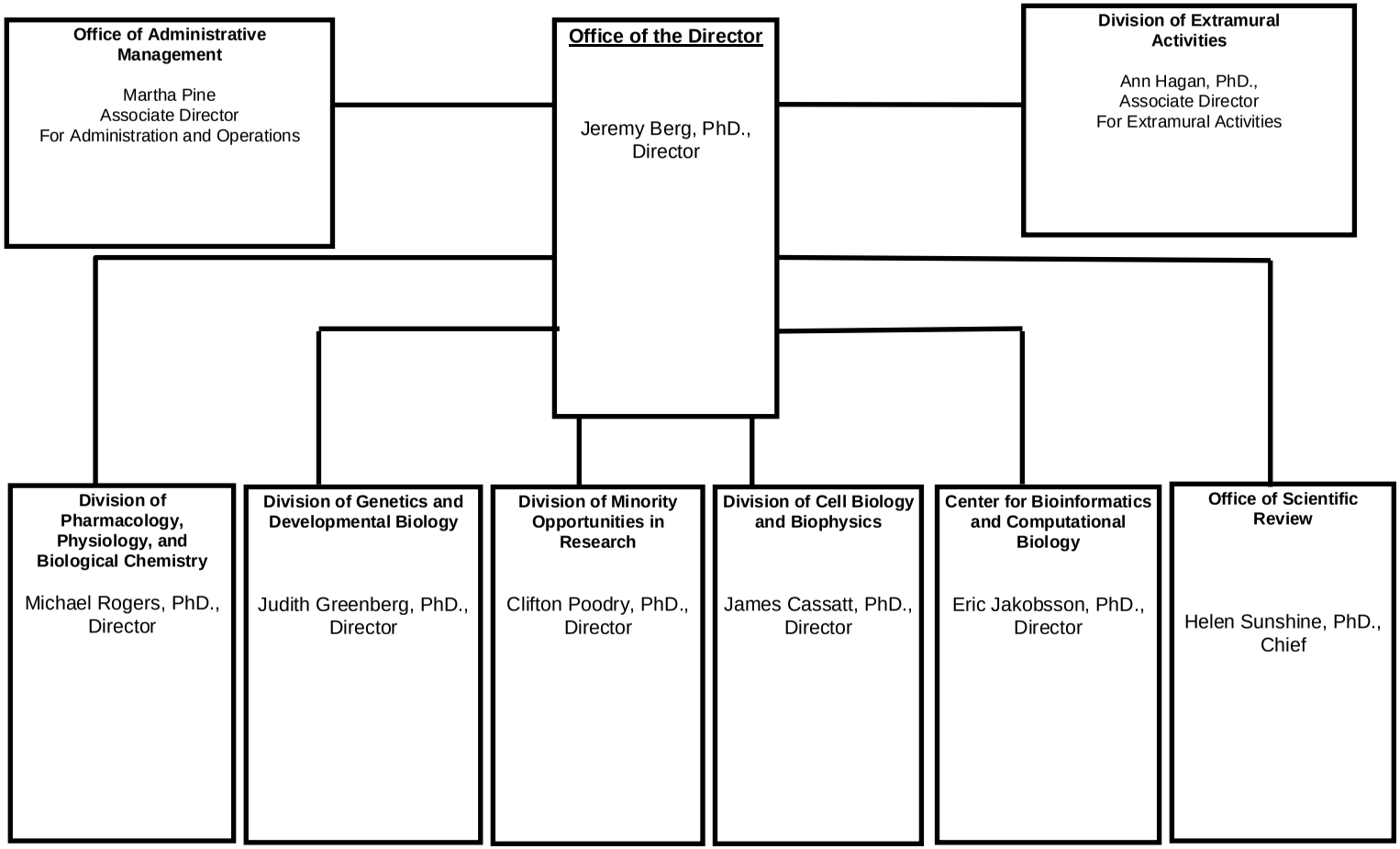
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For carrying out section 301 and title IV of the Public Health Service Act with respect to general medical sciences, [$1,959,810,000] $*1,955,170,000*.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act, 2005]

National Institutes of Health
National Institute of General Medical Sciences

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$1,916,333,000	$1,959,810,000	$1,955,170,000
Enacted Rescissions	(11,495,000)	(15,743,000)	0
Subtotal, Adjusted Appropriation	1,904,838,000	1,944,067,000	1,955,170,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	10,370,000	0	0
Comparative transfer to NIBIB for Radiology Program	(1,000)	0	0
Comparative transfer to Buildings and Facilities	(60,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	(10,370,000)	0	0
Subtotal, adjusted budget authority	1,904,777,000	1,944,067,000	1,955,170,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,904,777,000	1,944,067,000	1,955,170,000
Unobligated balance lapsing	(78,000)	0	0
Total obligations	1,904,699,000	1,944,067,000	1,955,170,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $208,000 FY 2005 - $500,000 FY 2006 - $500,000

Justification

National Institute of General Medical Sciences

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
124	$1,904,777,000	137	$1,944,067,000	137	$1,955,170,000	0	$11,103,000

This document provides justification for the Fiscal Year 2006 activities of the National Institute of General Medical Sciences (NIGMS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

This is an incredibly exciting time for biomedical science. Advances in technology are allowing researchers to examine the workings of complete biological systems, not just small parts of those systems. Scientists from quantitative disciplines like physics and engineering are contributing their expertise and approaches to biological studies, further widening the scope and speeding the pace of discovery. Computational tools and other resources are enabling scientists to share, integrate, and analyze the massive volumes of data their experiments generate. The rate at which basic research findings are translated into medical applications is accelerating. NIGMS has been instrumental in laying much of the groundwork for these developments, and the Institute's investments are paying off in significant ways.

One example is the detailed study of the system by which cells control the breakdown of unneeded proteins, a process that is as essential to life as its counterpart, protein synthesis. Knowing how cells balance protein synthesis and degradation is crucial for understanding how this equilibrium is disrupted in disease. NIGMS funds many scientists working in this area, among them Irwin Rose, Ph.D., of the University of California, Irvine, one of three winners of the 2004 Nobel Prize in chemistry. Rose has received nearly four decades of NIGMS support for fundamental biochemistry research that is now leading to drugs targeting the protein degradation pathway. The first such drug to be approved is Velcade, which was developed based on the work of another NIGMS-funded researcher, Alfred Goldberg, Ph.D., of Harvard Medical School in Boston, Massachusetts. Velcade is used to treat the blood cancer multiple myeloma and is showing promise in treating several other cancers.

In another example, tools created by NIGMS Protein Structure Initiative (PSI) scientists are revolutionizing the painstaking process of determining protein shapes, which is key to understanding how these cellular workhorses function. Robots, new methods of preparing materials for study, and other resources generated by the PSI have reduced the cost and time required for solving protein structures. Importantly, these advances and resources are benefiting the entire scientific community, not just those funded by the NIGMS initiative.

Further highlights of the scientific opportunities NIGMS offers, as well as the results of those opportunities and their relevance to medicine, appear in the following sections.

Story of Discovery: Exposing the M.O. of RNA Polymerases, Nature's Gene Decoders

To turn a tape-recorded interview into a newspaper story, journalists must first transcribe the sounds of a voice into words on a page. The cells in our bodies perform a similar task, transcribing information coded in the DNA of our genes into RNA, DNA's chemical cousin. The RNA is then translated into proteins, which perform much of the work in cells. The molecular machines responsible for gene transcription are enzymes called RNA polymerases.

The body contains trillions of cells, virtually all of which have exactly the same set of approximately 25,000 genes. Yet RNA polymerases selectively transcribe only those genes that are appropriate in each cell type, accounting for the differences between liver, nerve, muscle, and other cells. How RNA polymerases know which genes to express in a given cell and under a particular set of conditions has long been a major scientific mystery. Furthermore, the expression of genes in the wrong context can lead to cancer and other diseases.

For these reasons, a thorough understanding of how transcription works holds great promise for developing a broad range of molecular therapies, including potential adult and embryonic stem cell-based treatments. Another application of this knowledge, made possible by the sequencing of the human genome, is tracking gene expression patterns to monitor health and diagnose illness. Researchers are also targeting bacterial versions of the transcription machinery in their efforts to design urgently needed new antibiotic drugs.

Advancing the Case with Technological Improvements

Although biologists have been studying gene transcription by RNA polymerases since these enzymes were first discovered in 1960, details of how the enzymes work at a molecular level have remained elusive. For the most part, previous studies have been limited by the technology available to probe how the transcription process works. A primary reason these enzymes have been so difficult to study is their incredible complexity: RNA polymerases are not just single protein chains, but instead are giant assemblies of a dozen protein chains working together. In addition, they interact with many other accessory molecules that vary according to the cell's particular needs. Without knowing precisely what the many parts look like and how they interact, scientists have been unable to understand the way these intricate molecular machines work to perform their essential biological functions.

As a result of decades of NIGMS funding, scientists have built a substantial base of general knowledge on the transcription process. Technological advances are now providing great opportunities to break new ground in understanding RNA polymerase activity. In particular, NIGMS-sponsored efforts to introduce the application of physics and engineering techniques to biological problems have enabled researchers to examine the inner workings of RNA polymerase and to see single molecules of the enzyme in action.

A case in point is the work of Roger Kornberg, Ph.D., of the Stanford University School of Medicine in Stanford, California. After 20 years of unraveling the biochemistry and genetics of RNA polymerase, Kornberg used X-ray

crystallography to obtain a detailed, three-dimensional image of the enzyme that revealed the molecular tasks performed by each of its many parts. This achievement was greatly aided by a new robot system that automates the process of loading and positioning microscopic protein crystals on X-ray diffraction equipment. Jointly funded by NIGMS, the Department of Energy, and NIH's National Center for Research Resources, the robot is one of the high-throughput, or very rapid and efficient, techniques developed by the NIGMS Protein Structure Initiative.

The robot enabled Kornberg and his team to screen 130 crystals in a mere 7 hours without losing a single one. Done manually, this work would have taken many times longer, would have required considerable effort from highly trained scientists, and would have run an increased risk of losing delicate crystals due to human error. Once all of the crystals had been screened, the scientists collected data from the best ones, enabling them to determine the RNA polymerase structure with greater clarity than had ever been achieved before.

Widening the Investigation

All organisms, from bacteria to plants to people, have some form of RNA polymerase. Researchers like Seth Darst, Ph.D., of the Rockefeller University in New York City focus on understanding the RNA polymerases of bacteria. Darst used X-ray crystallography to show how bacterial RNA polymerase pulls apart the two strands of a DNA molecule, threading one strand into a narrow protein cavity and clamping it in place during transcription. The availability of structures from both bacterial and higher organisms provides a guide that may lead to new antibiotic drugs that attack the bacterial version of the enzyme without affecting the human enzymes. An example of an existing antibiotic that targets bacterial RNA polymerase is rifampicin, which is a key component of tuberculosis therapy.

The experiments described above required very small samples of RNA polymerase, less than one thousandth of an ounce. Even so, such samples still contain trillions of molecules, and the results reveal only the average behavior of molecules in this huge collection. Consider the rush of a crowd into an amusement park. Watching the group as a whole, it is impossible to discern the behavior of individual visitors. Similarly, in order to truly understand the mode of action of molecular machines such as RNA polymerases, scientists have been striving to develop methods capable of examining individual molecules in isolation.

Recently, Stanford University's Steven Block, Ph.D., applied techniques from physics and engineering to develop such methods. He observed single molecules of RNA polymerase in action and discovered that the molecules pause at some sites along the DNA for unusually long periods, ranging from seconds to tens of minutes. Block also discovered that when the enzyme detects a mistake during the transcription process, it backtracks, snips out the "typo," and inserts the correct chemical unit. This proofreading capability allows the enzyme to make RNA with remarkable fidelity, reducing the transcription error rate by 100 times or more.

The continuing explosion of insights and technological advances at the interface of biology, physics, and engineering will no doubt yield more evidence of the talents of RNA polymerases. This knowledge, in turn, will deepen understanding of the roles of these enzymes in maintaining health and point to ways of intervening when problems in transcription lead to disease.

Science Advances

These science advances convey the breadth and significance of NIGMS-supported research. Although only the lead scientists are named, coworkers and collaborators contributed substantially to the achievements.

Understanding Life Processes at the Molecular Level

Gene Silencing Illuminates Innate Immunity

Our world is teeming with potential health threats in the form of bacteria and viruses. Standing guard is the body's first line of immune defense, the innate immunity system. Despite the system's importance, researchers know relatively little about how innate immunity works. However, they have recently learned that the core molecular elements of innate immunity appear remarkably alike in organisms as diverse as plants, insects, and people. Thus, researchers are poised to answer key questions about this process by doing experiments in simple organisms.

In a recent example of the benefit of such an approach, Patrick O'Farrell, Ph.D., of the University of California, San Francisco, used laboratory fruit flies to search for fundamental clues about innate immunity. Harnessing the power of the revolutionary gene silencing technique called RNA interference (RNAi), which was featured in last year's story of discovery, O'Farrell used robotic methods to rapidly and systematically inactivate each of more than 7,000 fruit fly genes that are close counterparts of genes in humans and animals. He then identified those genes whose loss had a recognizable impact on the insects' ability to fight off germs. The strategy paid off, and O'Farrell discovered two fruit fly genes that are involved in carrying out the basic functions of innate immunity.

Since the fruit fly genes bear close resemblance to human genes, this work should quickly yield insights about how the proteins encoded by these genes function in human innate immunity. O'Farrell's findings are significant in another important way, as well. The results lend support for using RNAi to investigate complex molecular networks, which are known to be central to the function of both healthy and diseased cells.

Clarifying How Cells Connect

Connections between cells are critical for everything from embryonic development to holding the nervous system together. One of the ways that cells keep in contact is through fingerlike projections called neural cell adhesion molecules (NCAMs) that attach to the same molecules on neighboring cells. Exactly how these molecules bind to each other has been the subject of intense study, resulting in two, seemingly contradictory models. One model postulates that the NCAMs overlap just at their ends, as if the cells are touching each other by their fingertips. The other model supposes that the NCAMs overlap much more extensively, as if the cells are holding each others' hands palm to palm.

New research by Deborah Leckband, Ph.D., of the University of Illinois at Urbana-Champaign shows that both models are correct. Leckband measured the strength of the attachments between cell membranes at various microscopic distances and found that strong attachments occur at two clearly defined lengths, each corresponding to one of the competing models.

In addition to reconciling earlier research findings, Leckband's results offer fresh hints about how NCAMs work. The different bonding arrangements may reflect a two-step process by which cells adhere—as if first touching their fingertips before forming a tighter clasp. Alternatively, having two bonding configurations could allow cells to adjust their proximity to serve different needs. Studying how cells connect to each other not only sheds light on a critical

life process, it will also help scientists better understand—and someday perhaps prevent—birth defects and certain cancers.

Basic Studies Illuminate Disease Mechanisms

New Inhibitors Block Anthrax Toxin

In the fall of 2001, anthrax-contaminated letters sent through the mail caused 11 cases of inhalation anthrax, 5 of which were fatal. This bioterrorist attack focused national attention on the need for new ways to treat the previously uncommon infection, which is caused by the bacterium *Bacillus anthracis*. Unless antibiotics are administered quickly, they typically fail in treating inhalation anthrax because destroying the bacterium does not neutralize the effects of its three different toxins. One toxin, protective antigen, forms a tunnel through host cell membranes by which the other toxins, edema factor and lethal factor, enter and kill cells. Scientists have found that blocking the passage of lethal factor into cells reduces the severity of anthrax in animals, suggesting that this toxin is a good target for drugs against the disease.

Taking a different approach to foiling lethal factor, Lewis Cantley, Ph.D., of Harvard Medical School has devised a way to prevent the toxin from attacking cellular proteins. Cantley analyzed millions of small proteins to identify chemical inhibitors that latch onto and block the part of lethal factor that would otherwise attach to its targets.

The method worked. Cells in laboratory dishes that were treated with one of the inhibitors survived exposure to lethal factor, while untreated cells died. Cantley then determined the three-dimensional structures of lethal factor attached to several of the inhibitors, which enabled him to observe precisely how the inhibitors bind to the toxin. This information may now be used to design new drugs to combat anthrax.

Human Lung Cells Can Break Up Bacterial Gangs

While bacteria cannot speak or hear, their livelihood and ability to cause infections rest on effective communication skills. Large assemblies of networked bacteria called biofilms communicate by quickly trading chemical messages back and forth through a process known as quorum sensing. Scientists know that certain harmful bacteria use quorum sensing to evade the human immune system, and they also understand a good deal about how biofilms form and function. Until now, though, researchers were not aware that the human body could defend itself against quorum-sensing bacterial behaviors.

E. Peter Greenberg, Ph.D., of the University of Iowa in Iowa City discovered that one type of human lung cell, called an epithelial cell, has the means to cope with the potentially harmful quorum sensing that occurs within certain biofilms. He grew epithelial and other types of mammalian cells in laboratory dishes, then added molecules used in quorum sensing by *Pseudomonas aeruginosa*, the bacterium that causes most of the fatal lung infections in people with cystic fibrosis. Greenberg found that only the epithelial cells were capable of short-circuiting quorum sensing through the actions of an enzyme that blocked the bacterial signal.

The work is noteworthy because it suggests the existence of a built-in human defense system against certain serious bacterial infections, including those common in people with cystic

fibrosis. Scientists could capitalize on this new knowledge in searching for medicines to boost the body's natural ability to stop quorum-sensing signals. The research may also point to other innovative approaches to treating chronic infections linked to biofilm formation.

Cell Growth Protein Predicts Return of Prostate Cancer

Two men of the same age have been diagnosed with an advanced stage of prostate cancer. Both individuals follow their doctors' advice and undergo surgery to remove the malignant walnut-sized gland, which is involved in male reproduction. Although the patients are similar clinically, they may face different futures because the tests used to detect the cancer are poor predictors of whether the disease will return after removal. However, a close look at a protein present in many types of cancer cells reveals a new tool for forecasting a man's risk of prostate cancer recurrence.

Kun Ping Lu, M.D., Ph.D., of Beth Israel Deaconess Medical Center in Boston, Massachusetts, has spent years studying the protein Pin1, which helps regulate the growth and division of cells. He had previously shown that some types of cancerous tissue contain increased levels of Pin1.

Lu wondered if the Pin 1 levels he found in prostate cancer cells might signal the recurrence of the disease following surgery. To test this idea, he measured the amount of Pin1 contained in the malignant tissue removed by a single surgeon from hundreds of men diagnosed with prostate cancer. Lu then followed up with 580 of the men to find out if they were still cancer-free. This work revealed a link between levels of Pin1 at the time of surgery and prostate cancer recurrence. In fact, the higher the level of Pin1, the more likely it was that the disease would come back.

This finding suggests that doctors could measure Pin1 levels to predict their patients' chances of prostate cancer recurrence and to tailor the treatment plan. The results also indicate that drugs might be developed to suppress Pin1 levels, possibly preventing disease recurrence and further helping doctors manage what is now the most common cancer among American men.

New Approaches to Therapeutics

Hot Flash Drug May Interfere with Cancer Therapy

Tamoxifen (Nolvadex®) is an effective therapy for some types of breast cancer. However, roughly 80 percent of women who take the drug experience hot flashes. While not life-threatening, hot flashes can be so uncomfortable that people stop taking the medicine. To make this cancer-controlling drug tolerable, doctors can treat Nolvadex-triggered hot flashes with antidepressants such as paroxetine (Paxil®).

New evidence hints that taking both drugs together may not be such a good idea. David A. Flockhart, M.D., Ph.D., of the Indiana University School of Medicine in Indianapolis knew that the body uses the same enzyme to break down Nolvadex and Paxil. He therefore wondered whether taking both drugs together might affect blood levels of either or both of them. To test this, Flockhart performed a study with 12 breast cancer survivors who had been taking Nolvadex for at least 1 month and were having severe hot flashes. He gave Paxil to the study volunteers for 4 weeks and then took blood samples.

Women who took both drugs at the same time had substantially lower levels of a key byproduct of Nolvadex, chemical evidence that Paxil does affect how the body processes Nolvadex. But the effects differed among the women depending on their innate capacity to process drugs, which helps explain why Nolvadex's effectiveness can vary among people. Flockhart cautions that further data are needed to determine if treatment recommendations should be altered as a result of his study.

Bone Marrow Cells Help Heal Wounds, Maintain Skin

The body springs into action to heal a wound. Cells in the bloodstream muster to form a clot and fight infection. Researchers have long known that the infection-fighting cells are produced in the bone marrow. But recently, they discovered that cells from the bone marrow also play a role in healing wounds and maintaining normal skin.

Frank Isik, M.D., of the University of Washington Medical Center in Seattle tracked the fate of bone marrow cells by using mice whose cells were engineered to glow green under a fluorescent light. He transplanted green-glowing bone marrow cells from these mice into another set of mice, which were genetically identical except that they lacked the green fluorescent protein. He then inflicted a small wound in the skin of the transplanted mice's backs. To his surprise, as long as 6 weeks after the mice had been wounded, well after infection had ceased to be an issue, green-glowing cells derived from the bone marrow remained in their healed skin.

Probing further, Isik found that only the bone marrow-derived cells produced a particular type of collagen that is found in skin throughout the body, not just in healed wounds. This led him to conclude that cells from the bone marrow help form the tough, yet expandable, matrix of the skin. Isik now wonders whether diseases that interfere with wound healing, such as diabetes, do so because they affect bone marrow cells. In time, this line of research may reveal targets for drugs that will promote wound healing.

Promising Technologies

Sweeter Opportunities in Carbohydrate Research

Carbohydrates are not just a much-maligned food group, they are vital to all living systems. They take part in everything from communication between cells to the immune response, growth, and brain function. Made up of long, often highly branched chains of sugar molecules, carbohydrates are notoriously difficult for researchers to work with. As a result, the molecules are not nearly as well understood as DNA or proteins. Three recent advances reveal new insights into how carbohydrates work and how researchers can work with them. These findings promise to open new ways to diagnose and treat a host of diseases.

Ajit Varki, M.D., of the University of California, San Diego, has unexpectedly found that the carbohydrates people eat can actually infiltrate into their cells and may increase the risk of certain diseases. Previously, scientists believed that ingested carbohydrates were broken down into simple building blocks and that cells contained only carbohydrate molecules that the body synthesized from these smaller compounds.

Varki studied a carbohydrate molecule that is present in high levels in red meat and milk. Although humans do not make this carbohydrate, Varki had earlier found small amounts of it in human tissues. He has now shown that the source is meat and dairy products and that the molecule, which the body recognizes as alien, provokes an immune response that he believes could cause long-term inflammatory reactions in body tissues.

Eating large quantities of red meat has been linked to heart disease and some forms of cancer, and recent research suggests that meat in the diet may increase the risk for some autoimmune diseases like rheumatoid arthritis. Although most scientists think the primary culprit for such associations is saturated fat, Varki speculates that an immune response to foreign carbohydrates might also contribute.

Carbohydrates, like the one Varki studied, often coat the surfaces of cells, where they are crucial to cell interactions. Using a specially designed cell-surface carbohydrate, Carolyn Bertozzi, Ph.D., of the University of California, Berkeley, has accomplished the feat of tagging certain cells in living mice.

First, Bertozzi injected mice with an artificial carbohydrate that wended its way through their bodies, finally lodging on the outer surfaces of their cells. Then she fed the mice a chemical that reacts specifically with the synthetic carbohydrate but nothing else in their bodies. Taking advantage of the light-absorbing properties of the chemical tag, Bertozzi confirmed that the chemical had reached and reacted with the artificial carbohydrate, without causing any harm to the mice.

Bertozzi's ability to customize the carbohydrates on cell surfaces represents a powerful new way to study the molecules and promises a wide range of clinical applications, such as potentially tagging cancer cells with lethal chemicals.

To capitalize on opportunities like the one provided by Bertozzi, biotech and pharmaceutical companies will need to be able to synthesize carbohydrates efficiently. Currently, the process is labor-intensive and time-consuming. In a chemical *tour de force*, David MacMillan, Ph.D., of the California Institute of Technology in Pasadena developed a new method for building carbohydrates that is simple and straightforward, requiring just two steps. This technique will revolutionize the study of carbohydrates and could be used to produce a wide range of drugs and diagnostic tools, including those targeting the heart, immune system, and brain.

Still the most mysterious of biology's big molecules, carbohydrates have always been just as important as proteins and DNA to the lives of cells. Now, through these recent advances in tracking, customizing, and synthesizing carbohydrates, scientists are poised to understand the molecules better and use them in new medical applications.

Designing and Building Proteins Gets Easier

You may not be able to judge a book by its cover, but you can judge a protein by its shape. The three-dimensional structure of a protein, which is made of amino acids, enables it to latch onto other molecules, triggering a host of chemical reactions. When these reactions fail to occur properly, scientists search for the protein structure responsible. While they can easily determine

a protein's amino acid sequence, scientists cannot reliably predict how this sequence will fold into a protein with a certain shape and function.

Given this problem, some researchers have decided to work backwards. Rather than starting with a sequence, David Baker, Ph.D., of the University of Washington in Seattle started with a structure. In groundbreaking research, he showed that it is possible to design and build a protein with a specific shape. He sketched a protein structure that had never before been observed and then used a computer modeling program he had created to predict the amino acid sequence that would form the new molecule. Baker used that sequence to build an actual protein that was stable and quite similar in structure to the one he had drawn.

With this ability to create a protein made to order, Baker's research offers a promising new route for developing custom proteins that could be used as drugs or molecular machines to interrupt or enhance a particular reaction inside a cell.

NIH Roadmap

NIGMS has taken the lead in a number of NIH Roadmap initiatives in the "New Pathways to Discovery" and "Research Teams of the Future" themes. In concert with other NIH components, the Institute spearheaded the creation of National Centers for Biomedical Computing to develop the core of a universal computing infrastructure that is urgently needed to speed progress in biomedical research. The four centers funded in FY 2004 will create and make available software programs and other tools that will permit researchers to integrate and analyze data of different types and sources, blazing new pathways for understanding biological processes and human diseases.

The Institute also played a major role in the creation of Centers for Innovation in Membrane Protein Production to tackle the difficult issues surrounding the study of membrane proteins, which represent up to a third of all proteins and are the targets for a large number of therapeutic drugs. Two centers will develop new methods for producing significant amounts of membrane proteins for subsequent structural studies. To accelerate such studies, the centers will make their methods, materials, facilities, and data readily available to the scientific community.

Other Roadmap activities that were funded in FY 2004 include exploratory centers to develop high-resolution probes for cellular imaging and curriculum development awards in interdisciplinary research.

The imaging centers will develop greatly improved technologies to allow scientists to watch molecules move and interact in real time in living cells—information that will yield significant insights into the function of normal and diseased cells. These new technologies are needed to overcome the deficiencies of current imaging techniques, including limited resolution and a static, "snapshot" view of cellular components.

The curriculum development initiative supports innovative approaches to train biomedical, behavioral, and quantitative scientists to work in collaborative, interdisciplinary settings. The programs are expected to integrate disciplines in creative ways that could open new avenues of scientific inquiry and possibly lead to the formation of entirely new disciplines to address complex biological questions.

Additional NIGMS-led Roadmap activities focus on creating collections of diverse chemical compounds to use in identifying and validating targets for new drugs; developing methods for isolating, identifying, and modifying biologically active compounds from natural sources; improving ways of predicting the possible toxicity of compounds much earlier in the drug development process; and building exquisitely sensitive imaging tools to trace molecular pathways, particularly those involved in disease.

Initiatives

The vast majority of NIGMS grants support investigator-initiated studies in basic biomedical fields. These grants yield a wealth of new knowledge that forms the foundation for medical advances. The Institute also develops initiatives to catalyze research and new directions in areas of special interest or opportunity. Recent developments in several of these initiatives are described below.

Protein Structure Initiative

The NIGMS Protein Structure Initiative is an ambitious effort to improve understanding of the central role of proteins in health and disease. Its approach is to determine the structures of a large number of carefully selected, representative proteins that will serve as the basis for the much simpler and faster process of deducing the structures of related proteins based on their genetic sequences. Determining protein structures is highly worthwhile because it provides critical information about how proteins function and reveals new targets for the development of medicines.

The first phase of the PSI, which supports pilot centers that are assembling a pipeline for rapid protein structure determination, will end in FY 2005. At that time, the production phase of the initiative will begin. This phase will consist of several large centers that will determine the structures of many proteins very rapidly and efficiently. Additional, smaller centers will focus on particularly challenging classes of proteins, such as membrane proteins and proteins from humans. Another task will be to seek ways to overcome technological barriers to automated protein structure determination.

The pilot phase of the PSI has already led to marked improvements in the process of protein structure determination. For example, one of the nine PSI pilot centers solved 157 protein structures in less than 4 years, a remarkable feat in view of the fact that in the past, it took months to years to determine a single protein structure. In addition, this center cut the cost of determining a structure by two-thirds and expects further reductions in the cost and time required for structure determination.

The pilot centers, along with individual investigators who have PSI-affiliated research grants, have produced significantly enhanced methods and resources for the study of proteins. These include the robot system mentioned in the story of discovery above and robotic instruments for other stages of the structure determination pipeline. Companies are already developing some of these instruments for use by PSI researchers and the broader scientific community.

Among the other major technological advances made with PSI support is a method for data collection and processing that has slashed the time required for this step tenfold while more than tripling its accuracy. Two centers and one individual grantee have increased the success rate of the challenging process of protein crystallization—a necessary step for most structural studies—by developing three different methods of modifying proteins to promote the formation of crystals. Finally, a PSI scientist developed a process that greatly simplifies the production of proteins in bacterial cells, making it possible to produce ten times as much protein for study. This protein production breakthrough was recognized by *R&D Magazine* as one of the top 100 technological achievements of 2004.

An award also went to another PSI-related project, the massive upgrade of a synchrotron at Stanford University that was completed in early 2004. Synchrotrons are large facilities (about the size of a football field) that are crucial tools for studying the detailed structures of proteins and other molecules. NIGMS, the National Center for Research Resources, and the Department of Energy collaborated on funding the upgrade. Secretary of Energy Spencer Abraham gave the project the Secretary's Excellence in Acquisition Award in 2004 for completing the demanding effort ahead of schedule and within budget. The facility is actively promoting the use of robotic tools developed through the PSI, and users are reporting increases in the efficiency of their studies and the quality of their data as a result.

At the other end of the synchrotron scale, the PSI supported the development of a much smaller, table-sized synchrotron called the Compact Light Source. This technology could advance—and possibly revolutionize—structural biology research by allowing scientists to perform many studies without having to travel to one of the few national synchrotron facilities. The developers also envision medical imaging applications for the technology. Testing of the Compact Light Source prototype is scheduled to begin in early 2005.

Finally, NIGMS continued its partnership with the National Science Foundation, the Department of Energy, and other NIH components in funding the Protein Data Bank for a new 5-year period. This comprehensive, widely used public resource holds essential information on the three-dimensional structures of proteins and other large molecules, such as DNA and RNA. As of early November 2004, the Web-based repository contained data on nearly 28,000 structures, and the number is growing rapidly.

Complex Biomedical Systems Research

In FY 2004, NIGMS funded its fifth Center of Excellence in Complex Biomedical Systems Research. The new Center for Quantitative Biology at Princeton University in New Jersey will explore how biological molecules interact with each other and with their environment to create dynamic systems. The project will take a systems biology approach, using advanced computational methods to model complex biological systems based on large quantities of experimental data. To help spur further biomedical discoveries, the center will make all of its data and analysis tools freely available to the scientific community. The center will also establish a new undergraduate and graduate curriculum focused on quantitative biology and collaborative research.

This center is the latest embodiment of NIGMS efforts to move into new areas of science, foster multidisciplinary collaboration, and explore new approaches to biomedical research and research training.

Models of Infectious Disease Agent Study

In response to increasing concerns about emerging infectious diseases and bioterrorism, NIGMS made the first four grants in FY 2004 under its Models of Infectious Disease Agent Study (MIDAS) initiative. The multi-institution MIDAS teams are led by scientists at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland; Los Alamos National Laboratory in Los Alamos, New Mexico; Emory University in Atlanta, Georgia; and Research Triangle Institute International in Research Triangle Park, North Carolina.

MIDAS scientists will develop powerful computer modeling techniques to analyze and enhance the nation's ability to respond to infectious disease outbreaks, whether they occur naturally, such as SARS, or are released intentionally in a bioterrorist attack. In the event of a national medical emergency, MIDAS scientists will redirect their work to help government officials determine the best way to deal with the situation. MIDAS activities are guided by a steering committee and coordinated with related government efforts.

To quickly develop resources and collaboration within MIDAS, the steering committee requested that, in addition to the individual projects being conducted by each team, the network begin to study a problem together. The committee selected influenza as the first disease to model. MIDAS researchers plan to consider such variables as the structure of social networks and transportation issues in developing their models. To validate and fine-tune the models, the scientists will also attempt to computationally replicate historical outbreaks, such as the 1918 flu pandemic. With the unexpected reduction of U.S. flu vaccine supplies in late 2004 and the worrisome rise in avian flu cases in the Far East, the MIDAS flu models may have more immediate applications than had originally been anticipated.

Stem Cell Research

In FY 2004, NIGMS provided new administrative supplements to 15 research grants to enable investigators with little or no experience working with human embryonic stem cells to explore the use of these cells as a model system for research directly related to the aims of the parent grant. This brings the total number of new and continuing supplements funded in FY 2004 to 28.

The Institute plans to launch fellowships in human embryonic stem cell research in FY 2005. This effort addresses the need to train more skilled stem cell researchers, which the NIH Stem Cell Task Force has identified as a factor limiting the advancement of the field. The program would support postdoctoral fellows who show promise for becoming independent investigators as well as established scientists who wish to acquire new capabilities for studying human embryonic stem cells. Several other NIH funding components plan to participate in this activity.

NIGMS also plans to fund new Exploratory Centers for Human Embryonic Stem Cell Research in FY 2005. These centers will join the three that are currently funded.

The source of the stem cells for all NIGMS initiatives is limited to Federally approved stem cell lines listed on the NIH Human Embryonic Stem Cell Registry.

Large Grants Evaluation

During the 1990s, many members of the scientific community supported with NIGMS funding expressed an urgent need for grant mechanisms to support the collaborative, multidisciplinary team approaches needed to tackle complex problems of central importance to biomedical science. In response, NIGMS initiated several large grant programs including "glue grants," the PSI, the Pharmacogenetics Research Network, and centers for the study of complex biomedical systems.

Now that these programs have been operating for several years, NIGMS is developing plans to evaluate them. To this end, the National Advisory General Medical Sciences Council formed a working group that met for the first time in May 2004 and developed recommendations for assessing whether the programs are meeting their goals and whether any changes are needed to improve them.

Other Areas of Interest

Research Training

NIGMS continues its long history of leadership in the area of research training, supporting 45 percent of the predoctoral trainees and 26 percent of all of the trainees who receive assistance from NIH. In recognition of the rapidly changing, interdisciplinary nature of biomedical research today, the Institute's training programs are flexible and stress approaches to biological problems that cut across disciplinary and departmental lines. Such experience prepares trainees to pursue creative research careers in a wide variety of areas.

So that biomedical science can benefit from the broadest possible intellectual resources, NIGMS promotes the training of a scientific workforce that reflects the composition of the U.S. population. In addition to the special programs to increase the number of minority biomedical scientists described later in this section, the Institute requires its institutional training programs to document how they plan to recruit and retain underrepresented minority students and to report on the success of their efforts.

NIGMS trainees frequently contribute to significant research advances. For example, a research team that included NIGMS predoctoral trainees detailed the workings of a key enzyme that bacteria use to maintain the integrity of their cell walls. Because the bacteria studied are part of the family that causes diseases such as tuberculosis and leprosy, this research could lead to the development of much-needed new antibiotics to treat these diseases. Another group of NIGMS predoctoral trainees helped discover a cellular mechanism that prevents the immune system from overreacting to stimuli, which can lead to life-threatening, runaway inflammation. This finding suggests a promising target for treating a range of conditions in which the body's immune response spins out of control.

The Institute has several long-standing research training programs focused on areas with particularly pressing needs for well-prepared scientists. One of these, the Medical Scientist

Training Program (MSTP), supports training leading to the combined M.D.-Ph.D. degree and produces investigators who can bridge the critical gap between basic and clinical research. In addition to providing training in the biological, chemical, and physical sciences, the program encourages and supports training in computer science, social and behavioral science, economics, epidemiology, public health, bioengineering, biostatistics, and bioethics. In FY 2004, the MSTP supported 921 trainees through 41 institutional grants. Among the illustrious graduates of the program are two of the nine scientists who received inaugural NIH Director's Pioneer Awards in 2004: George Daley, M.D., Ph.D., of Children's Hospital in Boston, Massachusetts, and Joseph McCune, M.D., Ph.D., of the J. David Gladstone Institutes in San Francisco, California.

Another special program, the Pharmacology Research Associate (PRAT) Program, is NIGMS' only intramural activity. PRAT fellows conduct 3 years of postdoctoral research in NIH or Food and Drug Administration laboratories, working in such cutting-edge areas as neurobiology, tumor biology, and cell signaling. In FY 2004, a PRAT fellow working at the National Institute on Alcohol Abuse and Alcoholism published the results of a study that showed a difference between adolescents and adults in the activity of brain regions that motivate behavior to obtain rewards. This work has implications for understanding risk-taking and substance use in adolescents.

Other NIGMS training programs advance scientific progress by preparing researchers to enter the fast-growing fields of biotechnology, bioinformatics, and computational biology. The Institute's newest predoctoral training program is in biostatistics, a field that contributes to many biomedical research areas. For this reason, the program is being cofunded by a number of other NIH components. NIGMS anticipates making the first biostatistics training program awards in mid-2005.

Another new activity addresses the serious shortage of scientists who have the knowledge and skills required to study how organ systems and whole organisms respond to drugs and other physiological perturbations. The program encourages and funds short courses in this area, which has particular relevance to the fields of pharmacology, physiology, and toxicology. The first courses will be held in the summer of 2005.

Behavioral Research and Training

NIGMS funds basic behavioral research in such areas as the genetic and biochemical mechanisms underlying observed behaviors, neurobiology, drug metabolism, the mechanism of anesthetic action, and trauma and burn injury. Much of this research involves the use of model organisms, and NIGMS recently announced its interest in supporting the development of genetic tools and genomic resources that will enable researchers to exploit the full potential of such model systems.

The MIDAS program described above has a behavioral research element related to modeling the effects of social networks on the spread of infectious diseases. NIGMS is also participating in the NIH blueprint for neuroscience research, which has a significant behavioral component.

NIGMS funds research training in the behavioral sciences through institutional grants and individual fellowships, primarily in its medical scientist and systems and integrative biology

training programs as well as in programs administered by the NIGMS Division of Minority Opportunities in Research (MORE).

The Institute has followed with great interest the activities of a working group of the Advisory Committee to the Director, NIH, that was charged with reviewing the existing NIH portfolio of basic behavioral and social science research and identifying areas of opportunity consistent with NIH's mission that NIH should consider supporting. The working group, which presented a report at the December 2004 advisory committee meeting, was also charged with examining barriers to the submission and peer review of grant applications from researchers in the basic behavioral and social sciences. NIGMS plans to work closely with NIH leadership in responding to this report.

AIDS Program

NIGMS support related to AIDS falls into three areas: program project grants that fund structure-based drug design, AIDS-related research training in molecular biophysics, and research grants to improve the understanding of AIDS and its associated opportunistic infections.

NIGMS initiated its AIDS-related program project grants in FY 1987 to bring together crystallographers, chemists, and biologists to determine the detailed, three-dimensional structures of potential drug targets in HIV, the virus that causes AIDS. In recent years, several grantees have provided new insights into the structural basis of drug resistance in both HIV protease and HIV reverse transcriptase, the enzymes targeted by the majority of anti-HIV drugs. These studies have led to the latest generation of AIDS-fighting drugs, which have better resistance profiles than previous generations of drugs. This line of research can be expected to lead to even more effective drugs in the future.

The NIGMS research training program in molecular biophysics, which was established in FY 1988, prepares scientists to apply the techniques of physics and computer modeling to biological problems, chief among them HIV infection. Graduates of this program are trained to use structural biology in the design of drugs to fight HIV.

Minority Opportunities in Research

NIGMS has a long-standing commitment to increasing the number and capabilities of underrepresented minorities engaged in biomedical research. The focal point for this effort is the Division of Minority Opportunities in Research. The goal of the MORE Division is to encourage minority students to pursue training for scientific careers and to enhance the science curricula and faculty research capabilities at institutions with substantial minority enrollments. Through MORE's programs, NIGMS takes a leading role at NIH in research and research training activities targeted to underrepresented minorities.

The MORE Division has three components: the Minority Access to Research Careers (MARC) Branch, the Minority Biomedical Research Support (MBRS) Branch, and a section that handles special initiatives.

Minority Access to Research Careers

MARC supports student and faculty research training and enables institutions with substantial minority enrollments to strengthen their biomedical research training capabilities. As a result, these schools are able to interest students in, and prepare them for, pursuing doctoral study and biomedical research careers.

MARC offers Undergraduate Student Training in Academic Research (U*STAR) institutional grants, predoctoral fellowships, faculty predoctoral and senior fellowships, a visiting scientist program, and grants for ancillary training activities. MARC also manages a program of NIH predoctoral fellowships for minorities.

In FY 2004, MARC supported 648 undergraduate students at 58 institutions, 16 MARC predoctoral fellows, one postdoctoral fellow, two faculty fellows, and 139 NIH predoctoral fellows.

In response to the growing need for quantitative approaches to biological problems, MARC funded 13 grants in FY 2004 to enable institutions with U*STAR programs to plan for introducing or integrating the quantitative sciences into their biology curricula. The second phase of this program, which will support the implementation of successful plans, is expected to be announced in FY 2005.

Minority Biomedical Research Support

MBRS awards grants through three programs: Support of Continuous Research Excellence (SCORE), Research Initiative for Scientific Enhancement (RISE), and Initiative for Minority Student Development (IMSD).

SCORE assists biomedical research faculty at minority-serving institutions in developing competitive research programs that increase the number of underrepresented minorities who are engaged in biomedical research. RISE enhances the research environment at minority-serving institutions to increase the interest, skills, and competitiveness of students and faculty in pursuit of biomedical research careers. Institutions with established research programs can use IMSD support to initiate or expand activities that improve the academic and research capabilities of underrepresented minority students and facilitate their progress toward careers in biomedical research.

In FY 2004, 876 faculty members at 119 institutions worked on 408 research projects. MBRS also supported 1,335 undergraduate and 657 graduate students who worked as research assistants on scientific projects at their own institutions or in other settings, including laboratories at research-intensive institutions and in industry.

The MORE Division held a series of outreach meetings in FY 2004 with the directors of MARC and MBRS programs to discuss the current status of the programs and to solicit feedback from participants. The division is also using these meetings to assist in planning future program directions.

Special Initiatives

MORE supports several special initiatives that develop new approaches for the recruitment and retention of minority biomedical scientists. One such activity is Bridges to the Future, which is co-sponsored by NIGMS and the NIH National Center on Minority Health and Health Disparities. This program encourages students in associate's or master's degree programs to make the transition to the next level of training (the bachelor's or Ph.D. degree, respectively) toward careers in biomedical research. Since the program's inception in 1992, NIGMS has funded 159 grants, 9 of which received initial support in FY 2004.

The division also supports two innovative awards to foster the development of new skills. The MORE Faculty Development Award enables minority institution faculty members to update or enhance their research skills by spending a summer (or one academic term) every year for 2 to 5 years in full-time research at a research-intensive laboratory outside their home institutions. The Institutional Research and Academic Career Development Award combines a traditional postdoctoral research experience with an opportunity to develop teaching skills through mentored assignments at a minority-serving institution. The goals of the program are to provide a resource to motivate the next generation of scientists at minority-serving institutions and to promote linkages between research-intensive and minority-serving institutions that can lead to further research and teaching collaborations.

NIGMS continues to partner with the Indian Health Service to support Native American Research Centers for Health. This program encourages research on diseases and health conditions of importance to American Indians and Alaska Natives. It also prepares Native American biomedical and behavioral scientists and health professionals to compete for NIH funding. A third goal is to increase the capacity of both the research-intensive organizations and the Native American organizations to work together to produce competitive research proposals.

Another ongoing activity is the support of workshops, mini-courses, and meetings in a number of areas, including grant writing and program evaluation. For example, in FY 2004 the division collaborated with the University of Kentucky to develop an interactive, Internet-facilitated workshop on writing competitive grant proposals. This program is expected to launch in FY 2005.

Finally, the MORE Division awarded six grants in FY 2004 to support research that will test the effectiveness of interventions to increase minority and other student interest, motivation, and preparedness for biomedical and behavioral research careers. The long-term goal of the research supported by this program is to inform and optimize the design of MORE activities to promote entry into research careers.

Success Stories

In recognition of their exceptional achievements in nurturing minority students who are interested in research careers, two people associated with MORE programs were among the ten individuals who received 2004 Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring. They are Chellu S. Chetty, Ph.D., of Savannah State University in Georgia and Margaret Werner-Washburne, Ph.D., of the University of New Mexico in Albuquerque. Chetty directs an MBRS program and Werner-Washburne is an investigator on an

IMSD grant. Also honored was the American Physiological Society, which operates MORE-funded education and minority programs.

Many participants in MORE programs go on to productive research or research administration careers in academic, industry, or government settings. This shows that the educational strategy of involving students in hands-on research experiences is one that works. Recent success stories include:

- Annette Gabaldón, Ph.D., a former MBRS program participant at New Mexico State University in Las Cruces, is an assistant professor of biology at Colorado State University in Pueblo.

- Sixto Gonzales, Ph.D., a former MARC program participant at the University of Puerto Rico, Humacao, directs the Arecibo Observatory in Puerto Rico. He is also a senior research scientist and the assistant director for space and atmospheric sciences at the National Astronomy and Ionosphere Center.

- Marquea King, Ph.D., a former MARC program participant at Delaware State University in Dover, is a toxicologist with the Environmental Protection Agency in Washington, DC.

- Dale Lewis, Ph.D., a former MBRS program participant at the City University of New York, Bronx Community College, is a staff scientist with the National Cancer Institute, NIH.

Innovations in Management and Administration

NIGMS promotes innovations in management and administration to streamline work processes, respond to workforce and technology changes, and reduce paperwork and administrative burdens. A project that encompasses all of these areas involves automating the storage and retrieval of documents contained in official grant files.

The Institute piloted the use in some grant files of an electronic document management system developed by the National Cancer Institute. The success of the pilot led NIGMS to expand this effort to all of its grant files. The process entails merging electronic documents with scanned and uploaded versions of paper documents and then indexing the material. The transition to an all-electronic version of official grant files will enable NIGMS staff members to perform a variety of grant administration functions considerably more quickly and easily than is possible with paper files.

The NIH Neuroscience Blueprint

Overview -- The Blueprint is a framework to enhance cooperation among fifteen NIH Institutes and Centers that support research on the nervous system. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through initiatives and working groups focused on specific disorders. The Blueprint builds on this foundation, making collaboration a day-to-day part of how the NIH does business in

neuroscience. By pooling resources and expertise, the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

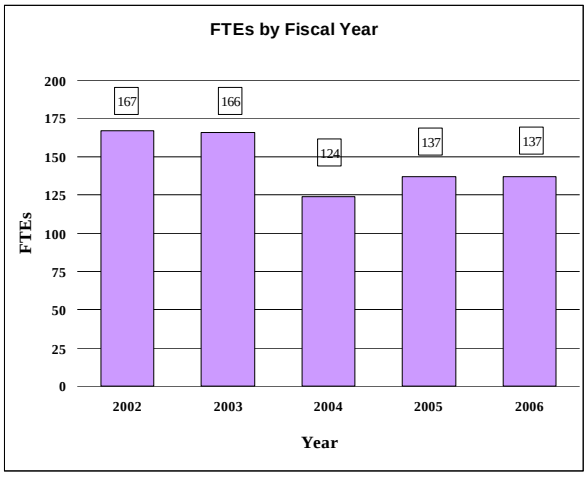
FY2005 -- For fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, include an inventory of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of ongoing gene expression database efforts.

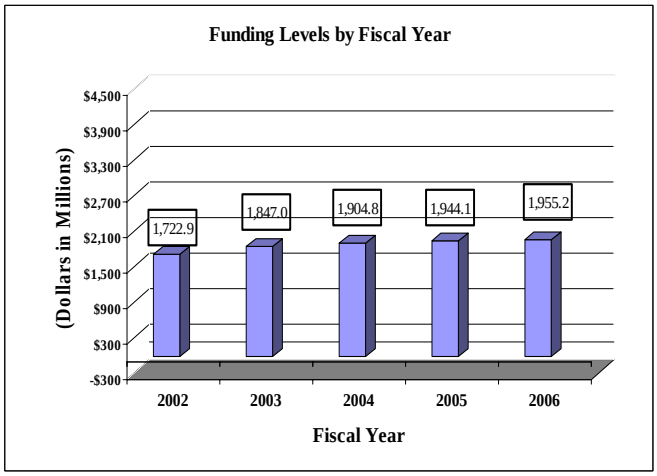
FY2006 -- Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Blueprint initiatives for fiscal year 2006 will include systematic development of genetically engineered mouse strains of critical importance to research on nervous system and its diseases and training in critical cross cutting areas such as neuroimaging and computational biology.

Budget Policy

The Fiscal Year 2006 budget request for the NIGMS is $1,955,170,000, an increase of $11,103,000 and 0.6 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NIGMS's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIGMS are shown in the graphs below:





NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $312,004,000 in FY 2006. While no inflationary increases are provided

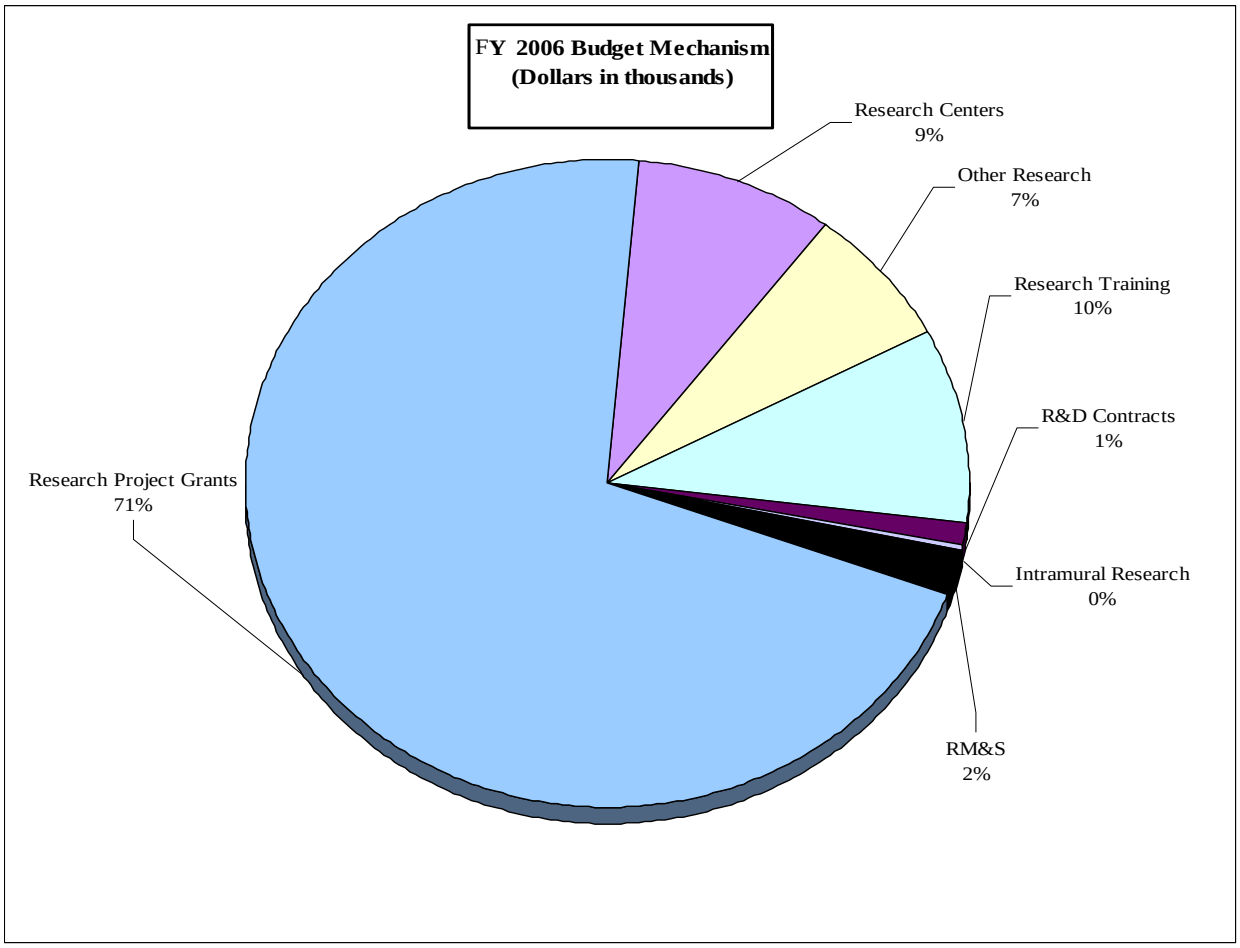
for direct, recurring costs in non-competing RPG's, where the NIGMS has committed to a programmatic increase in an award, such increases will be provided.

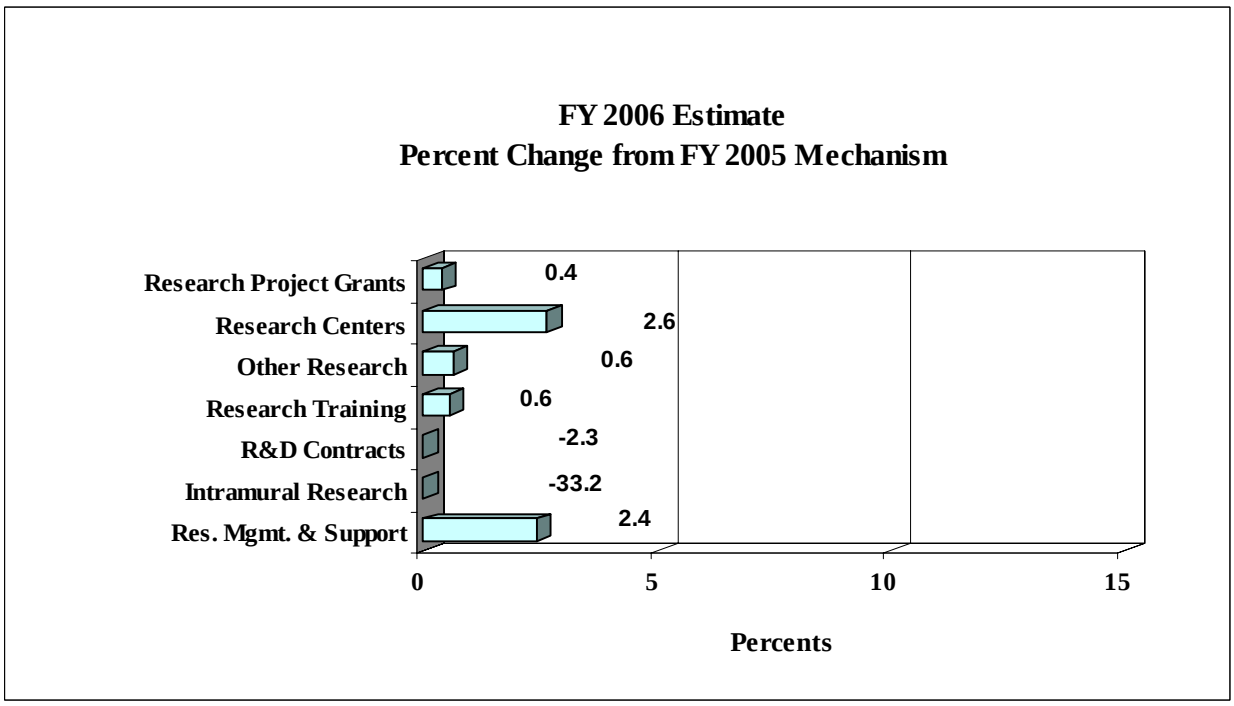
Advancement in medical research is dependent on attracting, training, and retaining the best and the brightest individuals to pursue careers in biomedical and behavioral research. In the FY 2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY 2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-docs with 1-2 years of experience are increased by 4.0%. This will bring these stipends closer to the goal NIH established for post-doc stipends in March, 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The increases in stipends and health insurance are financed within the FY 2006 request by reducing the number of Full-Time Training Positions, because NIH believes that it is important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research.

The Fiscal Year 2006 request includes funding for 57 research centers, 340 other research grants, including 76 career awards, and 26 R&D contracts. Intramural Research receives a decrease of 33 percent and Research Management and Support receives an increase of 2.4 percent.

NIGMS is participating in the NIH Neuroscience Blueprint. The FY 2006 request includes $100,000 for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project.

The mechanism distribution by dollars and percent change are displayed in the charts below:





NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Mechanism - Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,000	$973,045,000	3,006	$1,017,416,000	2,894	$1,008,542,000
Administrative supplements	(309)	20,637,000	(310)	20,904,000	(309)	20,627,000
Competing:						
Renewal	502	178,599,000	507	180,356,000	521	185,673,000
New	470	136,849,000	401	116,744,000	431	125,706,000
Supplements	6	468,000	8	624,000	8	625,000
Subtotal, competing	978	315,916,000	916	297,724,000	960	312,004,000
Subtotal, RPGs	3,978	1,309,598,000	3,922	1,336,044,000	3,854	1,341,173,000
SBIR/STTR	149	44,488,000	149	44,989,000	149	45,346,000
Subtotal, RPGs	4,127	1,354,086,000	4,071	1,381,033,000	4,003	1,386,519,000
Research Centers:						
Specialized/comprehensive	51	160,837,000	53	163,782,000	54	167,307,000
Clinical research	0	0	0	0	0	0
Biotechnology	1	2,853,000	1	3,339,000	3	4,318,000
Comparative medicine	0	432,000	0	491,000	0	428,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	52	164,122,000	54	167,612,000	57	172,053,000
Other Research:						
Research careers	57	11,666,000	71	13,951,000	76	14,717,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	36,000	0	46,000	0	53,000
Minority biomedical research support	154	102,104,000	154	102,104,000	154	102,104,000
Other	118	17,004,000	109	19,101,000	110	19,204,000
Subtotal, Other Research	329	130,810,000	334	135,202,000	340	136,078,000
Total Research Grants	4,508	1,649,018,000	4,459	1,683,847,000	4,400	1,694,650,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	594	24,040,000	584	23,878,000	570	23,878,000
Institutional awards	3,948	162,317,000	3,963	163,211,000	3,722	164,252,000
Total, Training	4,542	186,357,000	4,547	187,089,000	4,292	188,130,000
Research & development contracts	27	21,948,000	27	24,377,000	26	23,808,000
(SBIR/STTR)	(0)	(88,000)	(0)	(88,000)	(0)	(88,000)
	FTEs		FTEs		FTEs	
Intramural research	18	3,882,000	15	3,795,000	15	2,535,000
Research management and support	106	43,572,000	122	44,959,000	122	46,047,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, NIGMS	124	1,904,777,000	137	1,944,067,000	137	1,955,170,000
(RoadMap Support)		(6,540,000)		(12,241,000)		(17,484,000)
(Clinical Trials)		(0)		(0)		(0)

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual FTEs	FY 2004 Actual Amount	FY 2005 Appropriation FTEs	FY 2005 Appropriation Amount	FY 2006 Estimate FTEs	FY 2006 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Biomedical Research and Research Training		$1,857,323		$1,895,313		$1,906,588		$11,275
Subtotal, Extramural research		1,857,323		1,895,313		1,906,588		11,275
Intramural research	18	3,882	15	3,795	15	2,535	0	(1,260)
Res. management & support	106	43,572	122	44,959	122	46,047	0	1,088
Total	124	1,904,777	137	1,944,067	137	1,955,170	0	11,103

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Summary of Changes

FY 2005 Estimate				$1,944,067,000
FY 2006 Estimated Budget Authority				1,955,170,000
Net change				11,103,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$1,171,000		$22,000
b. Annualization of January 2005 pay increase		1,171,000		11,000
c. January 2006 pay increase		1,171,000		20,000
d. One less day of pay		1,171,000		(5,000)
e. Payment for centrally furnished services		153,000		1,000
f. Increased cost of laboratory supplies, materials, and other expenses		2,471,000		46,000
Subtotal				95,000
2. Research Management and Support:				
a. Within grade increase		14,254,000		250,000
b. Annualization of January 2005 pay increase		14,254,000		132,000
c. January 2006 pay increase		14,254,000		246,000
d. One less day of pay		14,254,000		(55,000)
e. Payment for centrally furnished services		11,891,000		59,000
f. Increased cost of laboratory supplies, materials, and other expenses		18,814,000		271,000
Subtotal				903,000
Subtotal, Built-in				998,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,006	$1,038,320,000	(112)	($9,151,000)
b. Competing	916	297,724,000	44	14,280,000
c. SBIR/STTR	149	44,989,000	0	357,000
Total	4,071	1,381,033,000	(68)	5,486,000
2. Research centers	54	167,612,000	3	4,441,000
3. Other research	334	135,202,000	6	876,000
4. Research training	4,547	187,089,000	(379)	1,041,000
5. Research and development contracts	27	24,377,000	26	(569,000)
Subtotal, extramural				11,275,000
	FTEs		FTEs	
6. Intramural research	15	3,795,000	0	(1,355,000)
7. Research management and support	122	44,959,000	0	185,000
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Building and Facilities		0		0
Subtotal, program		1,944,067,000		10,105,000
Total changes	137		0	11,103,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	137	137	0
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$148,233	$152,124	$3,891
Average GM/GS grade	12.3	12.3	0.0
Average GM/GS salary	$79,820	$82,215	$2,395
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$0	$0	$0
Average salary of ungraded positions	113,362	116,356	2,994

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$6,857,000	$7,141,000	$284,000
11.3 Other than Full-Time Permanent	5,352,000	5,574,000	222,000
11.5 Other Personnel Compensation	356,000	371,000	15,000
11.7 Military Personnel	0	0	0
11.8 Special Personnel Services Payments	0	0	0
Total, Personnel Compensation	12,565,000	13,086,000	521,000
12.0 Personnel Benefits	2,860,000	2,979,000	119,000
12.1 Military Personnel Benefits	0	0	0
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**15,425,000**	**16,065,000**	**640,000**
21.0 Travel & Transportation of Persons	430,000	425,000	(5,000)
22.0 Transportation of Things	53,000	52,000	(1,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	15,000	15,000	0
23.3 Communications, Utilities & Miscellaneous Charges	150,000	149,000	(1,000)
24.0 Printing & Reproduction	563,000	556,000	(7,000)
25.1 Consulting Services	79,000	78,000	(1,000)
25.2 Other Services	2,930,000	2,896,000	(34,000)
25.3 Purchase of Goods & Services from Government Accounts	85,021,000	84,271,000	(750,000)
25.4 Operation & Maintenance of Facilities	110,000	109,000	(1,000)
25.5 Research & Development Contracts	5,969,000	5,400,000	(569,000)
25.6 Medical Care	0	0	0
25.7 Operation & Maintenance of Equipment	773,000	764,000	(9,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**94,882,000**	**93,518,000**	**(1,364,000)**
26.0 Supplies & Materials	233,000	230,000	(3,000)
31.0 Equipment	471,000	471,000	0
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,831,845,000	1,843,689,000	11,844,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**1,928,642,000**	**1,939,105,000**	**10,463,000**
Total Budget Authority by Object	**1,944,067,000**	**1,955,170,000**	**11,103,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$6,857,000	$7,141,000	$284,000
Other Than Full-Time Permanent (11.3)	5,352,000	5,574,000	222,000
Other Personnel Compensation (11.5)	356,000	371,000	15,000
Military Personnel (11.7)	0	0	0
Special Personnel Services Payments (11.8)	0	0	0
Total Personnel Compensation (11.9)	**12,565,000**	**13,086,000**	**521,000**
Civilian Personnel Benefits (12.1)	2,860,000	2,979,000	119,000
Military Personnel Benefits (12.2)	0	0	
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**15,425,000**	**16,065,000**	**640,000**
Travel (21.0)	430,000	425,000	(5,000)
Transportation of Things (22.0)	53,000	52,000	(1,000)
Rental Payments to Others (23.2)	15,000	15,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	150,000	149,000	(1,000)
Printing and Reproduction (24.0)	563,000	556,000	(7,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	79,000	78,000	(1,000)
Other Services (25.2)	2,930,000	2,896,000	(34,000)
Purchases from Govt. Accounts (25.3)	27,652,000	26,902,000	(750,000)
Operation & Maintenance of Facilities (25.4)	110,000	109,000	(1,000)
Operation & Maintenance of Equipment (25.7)	773,000	764,000	(9,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**31,544,000**	**30,749,000**	**(795,000)**
Supplies and Materials (26.0)	233,000	230,000	(3,000)
Subtotal, Non-Pay Costs	32,988,000	32,176,000	(812,000)
Total, Administrative Costs	**48,413,000**	**48,241,000**	**(172,000)**

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Basic Behavioral Science – The legislative mandate for NIGMS specifically includes behavioral science research, although NIGMS does not now support behavioral science research or training. Given the wide range of fundamental behavioral topics with relevance to a variety of diseases and health conditions, the Committee encourages NIGMS to incorporate basic behavioral research as part of its portfolio, especially in the areas of cognition, behavioral neuroscience, behavioral genetics, psychophysiology, methodology and evaluation, and experimental psychology. (p. 127)

Action taken

In FY 2003, the National Institute of General Medical Sciences (NIGMS) provided $12.7 million in support of studies, primarily in model systems, to examine the genetic and biochemical mechanisms underlying behavior. This included research on the mechanisms underlying specific behaviors related to circadian rhythms, learning and memory, sensation and perception, pain and its management, and analgesia and anesthesia. Comparable levels of support were provided in FY 2004. A program entitled "Tools for Genetic and Genomic Studies in Emerging Model Organisms" was announced (http://grants2.nih.gov/grants/guide/pa-files/PA-04-135.html). The major goal of this PA is to support the development of tools to enhance the usefulness of DNA sequence information in research that includes behavioral studies. Such tools include microarray reagents, database management and data mining software, and improved methods for linking expression arrays with behavioral outcomes.

The Institute's research training programs mirror the areas of science that fall within the mission of the NIGMS. Several of the institutions supported through NIGMS' Systems and Integrative Biology (SIB) training grant program offer participants opportunities to pursue training in the basic behavioral sciences, and NIGMS highlighted the option of including behavioral science departments in SIB training programs when it recently updated its training program guidelines (see http://www.nigms.nih.gov/funding/trngmech.html#new_emphasis). In addition, individuals supported under the Institute's Medical Scientist Training Program (which leads to the M.D.-Ph.D. degree) may pursue research training in behavioral sciences if their institution offers that option. In both cases, the grantee institution chooses to offer this option as part of the multidisciplinary training mandated for all of NIGMS' training programs. NIGMS's individual fellowship support extends to fellows working on the molecular and genetic basis of behavior. In the past, some fellows have studied movement, sensation, and perception.

NIGMS is also exploring new areas of opportunity through its participation in a working group of the Advisory Committee to the Director, NIH, which has been formed to identify scientific

opportunities and areas of basic behavioral research that should be supported by NIH. A report of the working group is expected in December, 2004.

Item

Basic Research on Pre-Disease Pathways – As the NIH institute most concerned with basic research, NIGMS has provided leadership in research on physiological and biological structures and functions that may play roles in numerous health conditions. The Committee encourages NIGMS to collaborate with other institutes including NCI, NIMH and the Office of Behavioral and Social Sciences Research to fund research to integrate physiological knowledge of pre-disease pathways with behavioral studies. (p. 127)

Action to be taken

NIGMS, in collaboration with other components of the NIH, such as the National Institute of Mental Health, the National Cancer Institute, and the Office of Behavioral Social Sciences Research, is participating in a working group of the Advisory Committee to the Director, NIH, which was established to identify scientific opportunities and areas of basic behavioral research that should be supported by NIH. Discussion of NIH support of research to integrate physiological knowledge of pre-disease pathways with behavioral studies is one of many issues expected to be included in the group's discussions. The working group is expected to issue its recommendations in the form of a report in December, 2004.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	FY 2006 Amount Authorized	FY 2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,756,978,000	Indefinite	$1,767,040,000
National Institute of General Medical Sciences	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	a/		187,089,000		188,130,000
Total, Budget Authority				1,944,067,000		1,955,170,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997	936,573,000 2/	1,003,772,000	953,214,000 2/	998,387,000 3/
1998	992,032,000 2/	1,047,963,000	1,058,969,000	1,065,947,000
1999	1,111,439,000 2/4	1,150,840,000	1,197,825,000	1,197,825,000
Rescission				(799,000)
2000	1,194,068,000 2/	1,298,551,000	1,352,843,000	1,361,668,000
Rescission				(7,248,000)
2001	1,389,492,000 2/	1,548,313,000	1,554,176,000	1,535,823,000
Rescission				(125,000)
2002	1,720,206,000 2/	1,706,968,000	1,753,465,000	1,725,263,000
Rescission				(124,000)
2003	1,874,243,000	1,874,243,000 5/	1,853,584,000	1,859,084,000
Rescission				(12,084,000)
2004	1,923,133,000	1,923,133,000 5/	1,917,033,000	1,916,333,000
Rescission				(11,495,000)
2005	1,959,810,000	1,959,810,000 5/	1,975,500,000	1,959,810,000
Rescission				(15,743,000)
2006	1,955,170,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $83,000.
4/ Reflects a decrease of $3,447,000 for the budget amendment for bioterrorism.
5/ Reflects the President's Budget Request

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	10	11	11
Office of Scientific Review	9	10	10
Office of Administrative Management	24	24	24
Division of Extramural Activities	32	34	34
Division of Genetic and Developmental Biology	8	11	11
Division of Pharmacology, Physiology, and Biological Chemistry	24	26	26
Division of Cell Biology and Biophysics	9	11	11
Center of Bioinformatics and Computational Biology	2	3	3
Division of Minority Opportunities in Research	6	7	7
Total	124	137	137
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2002	10.7
2003	10.9
2004	12.3
2005	12.3
2006	12.3

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	1	1	1
Total - ES Salary	$143,498	$148,233	$152,124
GM/GS-15	10	10	10
GM/GS-14	15	16	16
GM/GS-13	19	20	20
GS-12	10	12	12
GS-11	5	7	7
GS-10	0	0	0
GS-9	5	5	5
GS-8	4	4	4
GS-7	3	3	3
GS-6	0	0	0
GS-5	1	1	1
GS-4	0	0	0
GS-3	0	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	72	78	78
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade			
Senior Grade			
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	0	0	0
Ungraded	58	68	68
Total permanent positions	71	77	77
Total positions, end of year	131	147	147
Total full-time equivalent (FTE) employment,end of year	124	137	137
Average ES salary	$143,498	$148,233	$152,124
Average GM/GS grade	12.3	12.3	12.3
Average GM/GS salary	$77,270	$79,820	$82,215