DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

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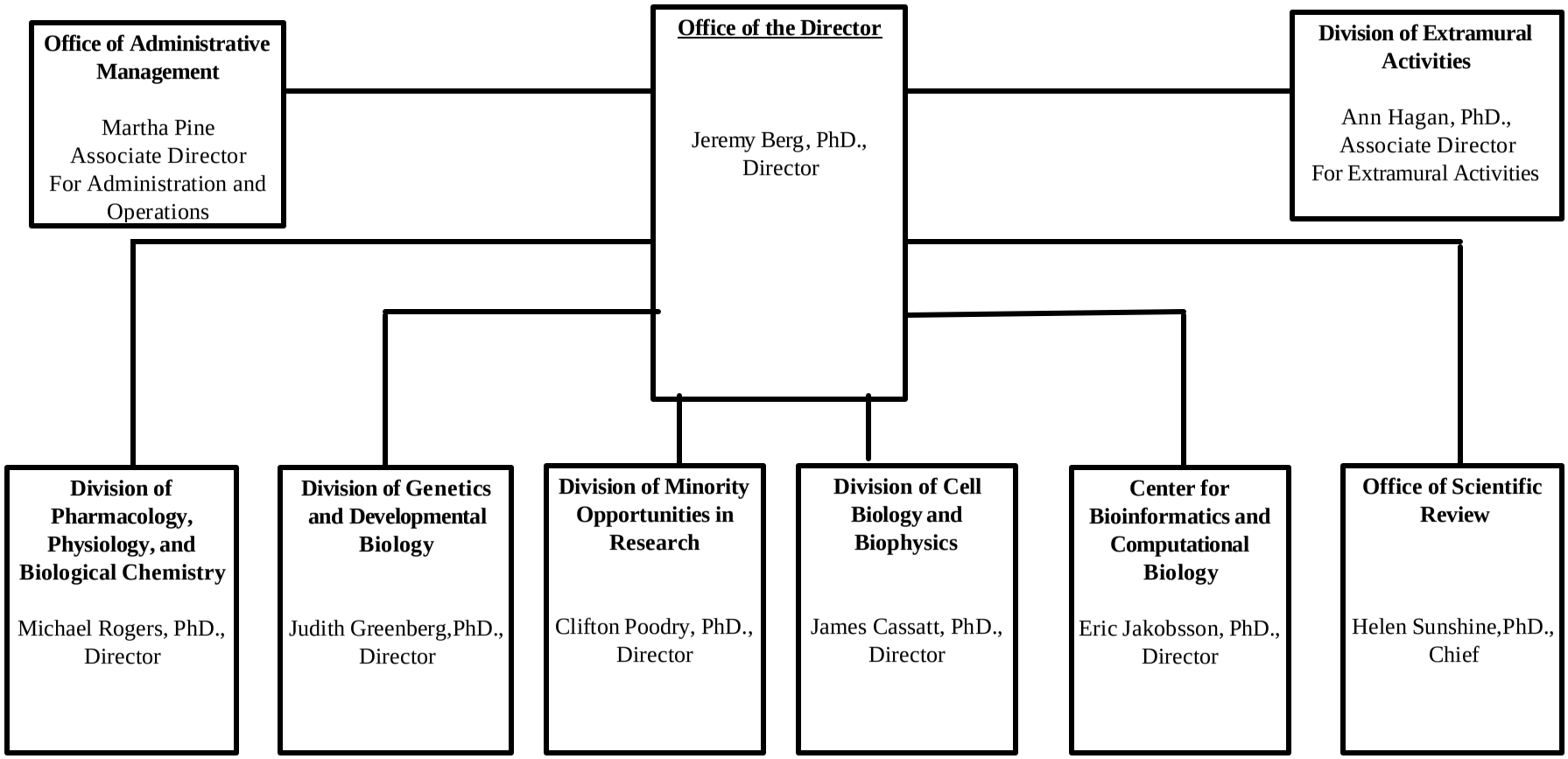
Organization Structure



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, [$1,916,333,000] $*1,959,810,000*.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004]

National Institutes of Health
National Institute of General Medical Sciences

Amounts Available for Obligation 1/

Source of Funding	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Appropriation	$1,859,084,000	$1,916,333,000	$1,959,810,000
Enacted Rescissions	(12,084,000)	(11,495,000)	---
Subtotal, Adjusted Appropriation	1,847,000,000	1,904,838,000	1,959,810,000
Comparative transfer to NIBIB for Radiology Program	(1,000)	(1,000)	(0)
Comparative transfer to Buildings and Facilities	(62,000)	(60,000)	(0)
Comparative transfer to Office of the Director for program changes	(195,000)	(0)	(0)
Subtotal, adjusted budget authority	1,846,742,000	1,904,777,000	1,959,810,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,846,742,000	1,904,777,000	1,959,810,000
Unobligated balance lapsing	(83,000)	---	---
Total obligations	1,846,659,000	1,904,777,000	1,959,810,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2003 - $113,000; FY 2004 - $255,000; FY 2005 - $255,000
Excludes $ in FY 2003 and $ in FY 2004 for royalties.

Justification
National Institute of General Medical Sciences

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
166	$1,846,742,000	166	$1,904,777,000	165	$1,959,810,000	(1)	$55,033,000

This document provides justification for the Fiscal Year 2005 research activities of the National Institute of General Medical Sciences (NIGMS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2005 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

NIGMS supports research that answers major questions about life, such as how cells live and die, how cells talk to each other, and how genes and proteins work. Other NIGMS studies focus on the way the body uses energy and how it responds to medicines. This research forms the foundation for new and better ways to diagnose, treat, cure, and prevent disease.

Some of the greatest mysteries about how the body works can best be tackled by large teams of scientists from different disciplines. NIGMS promotes this approach with grants that bring such teams together and speed the pace of discovery. Through these grants and other activities, the Institute is making special efforts to draw mathematicians, physicists, computer scientists, and engineers to biomedical research. Their expertise is especially needed to make the leap from studying individual molecules to understanding how molecules interact in complex biological systems. This knowledge will point to ways of intervening when these systems malfunction and illness results.

NIGMS plays additional key roles in maintaining the vitality of the scientific community by supporting the training of future researchers and working to increase the number of scientists who are members of underrepresented minority groups.

There are many indicators of the high quality of NIGMS-funded research ideas and scientists. One is the significant honors, such as Nobel Prizes and MacArthur Foundation "genius" awards, that regularly go to Institute grantees. A notable example is Roderick MacKinnon, M.D., who received the 2003 Nobel Prize in chemistry for determining the structure and function of ion

channels in cell membranes. Life and health depend on the proper functioning of these channels in transporting essential molecules like potassium and sodium into and out of cells. Insights from MacKinnon's studies could lead to ways to repair faulty channels to treat a wide range of diseases, including those affecting the heart and the nervous system. MacKinnon, a biophysicist at The Rockefeller University in New York City, continues to do exceptional research with NIGMS support. His most recent achievement is described in the Science Advances section of this document.

Another sign of the quality--and impact--of NIGMS research is the "breakthrough" designation given to scientific fields the Institute has nurtured. A case in point is the discovery and harnessing of a completely unexpected activity of the genetic material RNA. This exciting series of accomplishments is featured in the Story of Discovery that follows.

Story of Discovery:
Gene Silencing Tool Leads to New Understanding of Health and Disease

It is not every day that scientists reveal nature's best secrets, the ones that promise to deepen understanding of the biology of living things. The discovery of gene silencing by RNA interference (RNAi) is this kind of breakthrough. Researchers are using RNAi to reveal the function of genes in animals, plants, and humans. RNAi also offers a promising new approach to treating AIDS and a host of other diseases. Underscoring the importance of RNAi, *Science* magazine declared advances in this field to be the top scientific achievement of 2002.

Although scientists only discovered the existence of RNAi within the last decade, they now know that organisms have been using the process for millions of years. Researchers believe that RNAi's natural role is to tune the activity of genes, reducing their expression for purposes of growth and/or self-defense. When viruses infect cells, for example, they command their infected host to produce specialized RNAs to enhance viral survival. Researchers believe that RNAi is an ancient mechanism used to wipe away such unwanted, extra RNA, and some scientists speculate that it may even play a role in our immunity.

Unexpected Discovery

RNAi's use as a research tool began with an experiment gone wrong. Scientists studying the genetics of plant growth noticed a curious result. The researchers were attempting to deliver an extra "purple" gene to petunias, but the flowers instead bloomed stark white. The result evaded genetic logic and fascinated biomedical researchers, who yearned to understand how adding genetic material could somehow silence an inherited trait.

The mystery remained until, a few years later, two NIGMS-supported geneticists identified a similar process in animals. RNAi, they learned, operates like a molecular "mute button" to quiet individual genes. The two researchers, Andrew Fire, Ph.D., of the Carnegie Institution of Washington in Baltimore and Craig Mello, Ph.D., of the University of Massachusetts Medical School in Worcester, had been using a molecular tool called antisense RNA to dampen gene activity in roundworms and tease apart genetic factors that contribute to cell growth and tissue formation. In this technique, researchers cause the normally single-stranded RNA to bind to an opposite, or "anti-," strand. This blocks the RNA from delivering the instructions to make a protein.

To their surprise, Fire and Mello discovered that the activity of their laboratory preparation did not depend on the antisense RNA itself, but instead on a contaminant that was produced during the synthesis of the antisense RNA. The contaminant, it turns out, was a molecule of double-stranded RNA. Fire and Mello quickly learned that they could mute specific genes simply by feeding their experimental worms double-stranded RNA with the same sequence as the gene they wished to target.

RNAi All Around

RNAi took the research world by storm. NIGMS grantee Gregory Hannon, Ph.D., of Cold Spring Harbor Laboratory on Long Island, New York, dropped everything he was doing when he learned that RNAi could be used as a tool in fruit flies as well as worms. Using this popular insect model system, Hannon has uncovered a link between RNAi and Fragile X syndrome, which is the most common inherited form of mental retardation. Also at Cold Spring Harbor Laboratory, NIGMS grantee Shiv Grewal, Ph.D., led a team that discovered RNAi's pivotal role in the normal functioning of yeast cells, which share many features with the cells of humans. Grewal, who is now at the National Cancer Institute, has learned that the molecules that normally carry out RNAi help to organize chromosomes so they can be pulled apart during cell division, one of the most basic steps in the lives of all cells.

Basic scientists investigating gene function began to try RNAi in other organisms and found that the technique could be applied nearly universally to manipulate gene activity in many different model systems. However, researchers had sporadic and unpredictable success getting RNAi to work in cells from mammals. In 1999, the situation brightened when Hannon's group and a team of NIGMS-supported scientists from the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts--including David Bartel, Ph.D., Phillip Sharp, Ph.D., Thomas Tuschl, Ph.D., and Phillip Zamore, Ph.D.--developed systems for conducting RNAi experiments in a test tube. Collectively, these approaches revealed RNAi's molecular *modus operandi* and led the way toward getting the technique to work in mammalian cells. The researchers learned that in RNAi, the double-stranded RNA is first chewed up into smaller RNA pieces by a newly discovered enzyme named Dicer. The scientists realized that RNAi silences gene activity through the action of these tiny RNA snippets, which they dubbed short interfering RNAs (siRNAs).

RNAi to the Rescue

Researchers predict that in addition to RNAi's potential for solving many of the mysteries encoded in our genes, the technique holds promise for new therapies. NIGMS grantee Yang Shi, Ph.D., of Harvard Medical School in Boston, Massachusetts, is one of several researchers who have crafted clever tools for getting living cells to produce specific siRNAs. These methods have greatly enhanced researchers' ability to explore RNAi's medical promise in mammalian cells. For example, in recent lab tests with isolated cells, Sharp and others have succeeded in using RNAi to kill HIV, the virus that causes AIDS. Biologists are now working hard on the very challenging problem of developing ways to deliver siRNAs to the body in order to make RNAi a practical means for treating, and perhaps preventing, 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

Discovering How Cell "Doors" Open and Close

Cells don't let just any substance slip through their protective external membranes. Most substances must first convince cells to open their doors to allow them in or out. Scientists have known for years that electrically charged particles, such as sodium and potassium ions, can pass across a cell's membrane through tunnel-like protein structures known as ion channels. Ion channels are critical to many biological processes, such as the beating of the heart, nerve

impulses, digestion, and insulin release. But until recently, the precise mechanisms by which cells open and close these doors to the outside world have largely remained a mystery.

In a continuation of his Nobel Prize-winning ion channel research, Roderick MacKinnon has recently determined the three-dimensional structure of a "voltage-dependent" potassium channel. His findings have challenged the previously accepted view of how these channels sense voltage changes across the cell membrane. The segment of the channel that acts as the sensor turns out to extend into the membrane itself rather than being tucked in on the inner surface of the channel, as had been believed. The sensor is pulled from one side of the membrane to the other when the voltage changes. In turn--through a process not yet understood--the sensor pulls on other parts of the channel, causing it either to open or close. The sensor thus responds to voltage changes much like the button of an automatic door responds to pressure: It senses the stimulus and brings about a response.

Nigel Unwin, Ph.D., a cell biologist at The Scripps Research Institute in La Jolla, California, has been studying a different type of ion channel: one that responds to a chemical, rather than an electrical, stimulus. He has found that this channel, called the acetylcholine receptor, has door-like segments in its middle that, when closed, block the flow of ions. The doors are attached to the rest of the channel through hinge-like regions around which they can rotate. When the chemical messenger binds to the channel, the doors open, allowing ions to pass through.

A deeper understanding of the workings of ion channels may allow scientists to develop new drugs for conditions ranging from heart disease to diabetes.

Clues to Why Old Eggs Fail

Older women are more likely to give birth to children with Down syndrome, a form of mental retardation. The condition is caused by the presence of three copies, rather than the standard two copies, of chromosome 21 in human cells. This problem in chromosome distribution, called meiotic nondisjunction, occurs in the course of the cell division that gives rise to eggs (as well as to sperm). But no one knows how or why meiotic nondisjunction increases as eggs age. The question has been difficult to answer because scientists were unable to develop an animal model in which to study the condition.

Now, Sharon Bickel, Ph.D., a molecular biologist at Dartmouth College in Hanover, New Hampshire, has developed a method that uses fruit flies to gain insight into this puzzle of human biology. Fruit flies continuously produce eggs, but Bickel manipulated the diet of the flies in a way that suspended the maturation of their eggs, allowing them to "age." This mimicked the aging of human eggs.

Studying the "aged" fruit fly eggs, Bickel found that the incidence of meiotic nondisjunction jumped just as it does in older women. Her work also indicated that a back-up genetic system that normally helps to ensure proper chromosome separation and distribution deteriorates as fruit fly eggs age. No one yet knows if the same back-up system exists in humans, or if identical

mistakes account for the increased risk of Down syndrome in the children of older mothers. But the fruit fly model system will allow Bickel and others to investigate these important questions.

RNA Changes Guide the Nervous System

The four chemical building blocks of DNA connect in various orders, or sequences, to form genes. Our genes carry the instructions for making proteins, which perform thousands of different tasks in our bodies. In reading a particular gene's instructions and making the protein it specifies, a cell creates an intermediate molecule called messenger RNA (mRNA). This molecule's sequence usually exactly reflects the gene's sequence. But in certain cases, cellular enzymes can "retype" a portion of an mRNA's sequence. This "edited" mRNA template causes the cell to produce a completely different protein than the original gene specified. The new protein often has a different function.

Geneticist Robert Reenan, Ph.D., of the University of Connecticut Health Center in Farmington has developed a new approach to search for edited genes. In doing so, he discovered that the process is not as rare as was once believed. Reenan compared the sequences of an edited gene in 18 species of experimental fruit flies. He noticed a preserved pattern, or signature, in all of the versions of the gene. Reenan suspects that the signature translates into a common RNA shape that is easily recognized by RNA editing machinery in the cell. Looking for other fly genes that may contain the editing signature, he evaluated the spellings of more than 900 genes in just two fruit fly species and discovered 16 additional genes that undergo editing. He found that all of the newly discovered editable genes spell out proteins used for super-quick electrical or chemical transmission by the fruit fly nervous system.

Reenan's discovery may help explain how the nervous system can adapt rapidly to changes in our surroundings by permitting cells to make quick edits to gene copies (in the form of mRNA) rather than to the original DNA. A more thorough interpretation of the language scripted in genes central to nervous system function may help researchers find new ways to diagnose and treat a variety of neurological diseases known to have a genetic component, such as Parkinson's disease, Alzheimer's disease, epilepsy, and many others.

Basic Studies Illuminate Disease Mechanisms

Cell Death Research Uncloaks Deadly Virus Action

Death is vital to life, especially when your body needs to get rid of worn-out or unneeded cells. This essential housekeeping job is performed by an elaborate biochemical process called apoptosis, or programmed cell death. However, under certain conditions, apoptosis can go awry, leading to life-threatening illnesses.

Scientists studying fruit flies have discovered various proteins involved in apoptosis, including the aptly named Grim and Reaper proteins. To find out what proteins with similar functions exist in other species, pharmacologist Sally Kornbluth, Ph.D., of Duke University Medical Center in Durham, North Carolina, searched through databases cataloging the DNA sequences

of proteins. What she found was a protein resembling Reaper in a family of infectious agents called Bunyaviruses.

It was an important finding, since Bunyaviruses are the major cause of two potentially fatal insect-transmitted diseases in humans: hemorrhagic fever and pediatric encephalitis. Like Reaper, the Bunyavirus protein--dubbed NSs--appears to deal its deadly blow in part by promoting apoptosis. Studies in mice by Kornbluth's team show that NSs causes massive death of brain cells--an observation that could help explain the severe brain inflammation in people with hemorrhagic fever and pediatric encephalitis.

Interestingly, the discovery of these potent proteins could also shed light on why viral encephalitis is so serious in infants. Based on her studies, Kornbluth suggests that Bunyaviruses may hijack the normal processes of cell death that are particularly active during the early wiring of young nervous systems. Further research is now under way in her lab to figure out the precise mechanism by which NSs proteins act. By understanding these mechanisms, scientists hope they can one day develop better ways to treat viral encephalitis and other dangerous diseases in which these proteins may be involved.

Inherited Susceptibility to Meningococcal Disease

Meningococcal disease is a potentially fatal illness caused by the bacterium *Neisseria meningitidis*. This bacterium is commonly found in the noses and throats of healthy people, but occasionally it invades the fluid surrounding the brain and spinal cord and causes meningitis. Worse still, the bacterium may seep into the bloodstream, causing meningococcal sepsis, an overwhelming, generalized blood infection. Neither scenario is good news: 2 percent of those who develop meningitis die from the infection, while the fatality rate for those who come down with meningococcal sepsis is 12 percent. Roughly 2,400 cases of meningococcal disease occur in the United States annually, and most of its victims are infants or young adults.[1] Given that *Neisseria meningitidis* is harmless to most of us, scientists have long suspected that a person's genes play a role in determining whether or not meningococcal disease will develop.

Bruce Beutler, M.D., an immunologist at The Scripps Research Institute, has been studying a family of genes that is involved in "innate" immunity, the body's initial, broad defense response to invading microbes. These genes, called the Toll-like receptors (TLRs), were discovered in fruit flies, and it was in this insect model system that TLRs were first found to be involved in providing immunity.

One TLR that Beutler has taken a particular interest in, toll-like receptor 4 (TLR4), binds to a molecule on the exterior surface of *Neisseria meningitidis* bacteria. TLR4 sounds an early alarm when the bacteria breach our barriers, summoning immune cells to destroy the invaders. A defect in TLR4 could potentially allow the bacteria to get a toe-hold and lead to an overwhelming infection.

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[1] Rosenstein NE, Perkins BA, Stephens DS, et al., The Changing Epidemiology of Meningococcal Disease in the United States, 1992-1996. J Infect Dis 180:1894-1901, 1999.

By comparing the DNA sequences of 220 people who had had meningococcal disease with the sequences of 283 healthy control subjects, and using special software he designed, Beutler identified a number of rare variations in TLR4 that correlated with susceptibility to the disease. His results suggest that these variant sequences predispose a person to meningococcal disease by impairing the ability to respond in the first minutes or hours of a bacterial invasion.

In addition to providing evidence for a genetic basis to meningitis susceptibility, Beutler's findings pave the way for the development of diagnostic tests for those at risk. In the future, preventive treatment could be given to those with risk-increasing TLR4 mutations prior to surgery or travel to areas where meningococcal disease epidemics are in progress. In addition, the approach that Beutler has pioneered may be applied to the study of other diseases in which both genes and environment play a role.

Cell Stress May Contribute to Neurological Diseases

People respond to stress or heat by sweating; cells respond by activating heat shock proteins that help repair or clear damaged proteins. Research by cell biologist William Welch, Ph.D., of the University of California, San Francisco, has illuminated an important connection between heat shock proteins and nine devastating neurological diseases, including Huntington's disease.

Scientists know that all of the diseases are associated with mutant proteins that form clumps in nerve cells, leading to the cells' death. Welch used mouse cells to study one of these diseases, spinobulbar muscular atrophy (SBMA). In SBMA, clumping of the mutated proteins activates the cell's stress response system, generating heat shock proteins that would normally rid the cell of the malformed proteins. Welch found that the protein clumps grab the heat shock proteins before they can do their work, permanently activating the stress response system. This generates still more heat shock proteins, which are in turn pulled out of commission by the clumps.

In addition, Welch discovered that cells damaged in this way are extremely sensitive to various kinds of stress, including heat and different toxins. His experiments showed that only half of the cells with the clumped proteins survived a temperature increase that normal cells could tolerate. Moreover, the abnormal cells that did survive experienced further clumping. These results suggest that physiological or environmental stress may play a role in initiating and/or accelerating this group of neurological diseases. Welch is now using laboratory mice to test whether stressed animals do indeed develop SBMA more quickly than do non-stressed animals.

New Approaches to Therapeutics

Gene Silencing Studies Yield Potential New Class of Anticancer Drugs

Everything from the genes you inherit to what you eat, the air you breathe, and how much you exercise influences the development of cancer. But the disease ultimately results from chemical changes to DNA that spur cells to grow and divide uncontrollably. One of these changes is called DNA methylation, which in normal cells "silences," or shuts off, genes that are not needed in particular cell types or under certain conditions.

In some cancer cells, however, abnormal DNA methylation shuts off tumor suppressor genes, which normally put the brakes on cell growth and division. Since turning these genes off opens the door to uncontrolled cell growth and cancer, scientists have long hoped that chemicals that inhibit DNA methylation would one day prove useful as anticancer drugs. But the toxicity and instability of these chemicals have dogged drug-development efforts.

Now, thanks to a study that began with a commonly studied laboratory fungus, a new DNA methylation inhibitor is under investigation as a potential anticancer drug. Molecular biologist Eric Selker, Ph.D., of the University of Oregon, Eugene, initially discovered that a molecule called zebularine reverses DNA methylation in the fungus. He went on to show that zebularine also reverses DNA methylation and reactivates a tumor suppressor gene in human bladder cancer cells grown in the laboratory. Selker then injected these cancer cells into mice and gave them zebularine orally. The molecule reduced tumor size in the mice, making zebularine the first DNA methylation inhibitor to have such an effect in animals.

Zebularine is unique among the DNA methylation inhibitors that have been studied to date because it is chemically stable, can be administered orally, and appears to be minimally toxic. Its only side effect seems to be a slight weight loss in the mice given the chemical. These favorable properties suggest that zebularine may be a good candidate for drug development and that it could be a prototype for a new class of anticancer drugs. Selker's university has filed a patent on the potential uses of zebularine and is currently working to develop it into a marketable drug.

Copper Transporter Is Key to Cisplatin Drug Resistance

Nearly half a century ago, a stroke of luck led scientists to discover the cancer drug cisplatin. Researchers investigating the effect of electrical fields on bacterial growth discovered that a metal-containing chemical solution used to conduct current, not the electrical fields themselves, stopped the bacteria from dividing. Further tests proved that cisplatin, a platinum-containing substance produced when the metal electrodes reacted with the chemical solution, could also halt the growth of cancer cells. Today, cisplatin is an important component of the treatment for many advanced testicular and ovarian cancers. However, tumor cells can "learn" how to reject cisplatin and other chemotherapy drugs, allowing the cells to multiply and spread. Doctors cannot simply give more cisplatin to remedy this drug resistance problem because of the risk of serious ear and kidney toxicities caused by higher doses of the drug.

Basic researchers studying the role of metals in biology have made another surprise discovery about cisplatin. An interdisciplinary team of scientists found what is likely to be a main cause for cisplatin resistance, and it has to do with how the body handles another metal: copper. Biochemist Dennis Thiele, Ph.D., of the University of Michigan Medical School in Ann Arbor and the late geneticist Ira Herskowitz, Ph.D., of the University of California, San Francisco, joined forces to discover that the Ctr1 protein, which transports metals into cells, takes in not only copper, but also cisplatin. The researchers found that yeast cells that lacked the metal transporter protein were highly resistant to cisplatin, suggesting that the cells had no way to absorb the drug. The scientists next created experimental cell lines using mice that lack the

equivalent copper-intake protein. Mouse cells that did not contain any Ctr1 protein were eight times more resistant to cisplatin than their normal counterparts.

Since human Ctr1 is 92 percent identical to mouse Ctr1, it is highly likely that the metal transport protein works the same way in mice as it does in humans. The researchers reasoned that a defective or missing copy of the gene that codes for Ctr1 in some tumor cells may explain why certain people stop responding to cisplatin. The findings have important medical implications: If researchers can figure out a way to increase the amount or activity of Ctr1 in tumor cells, they may be able to extend the use of this effective chemotherapy drug. Future pharmacogenetic studies, in which scientists search for connections between genes and drug response, may help identify who will respond well or poorly to cisplatin treatment.

Botulinum Toxin Study May Lead to Inhaled Vaccine

Botulinum toxin (BT) is the single most poisonous substance known, with very small amounts causing paralysis and death.[2] Botulism, the illness caused by this bacterially produced toxin, typically results from eating contaminated food. Cases of botulism are rare, but concerns about the possible use of BT as a bioterrorism agent have brought a new urgency to research in this area. Of special interest is the effect of inhaling the toxin.

Biochemist Lance Simpson, Ph.D., of Jefferson Medical College in Philadelphia concluded that inhaling BT can cause poisoning when the toxin travels from the airways to the bloodstream, where it does widespread damage to the body. He also discovered that a piece of the BT protein called the heavy chain was an effective inhaled vaccine in experimental mice. Simpson vaccinated the mice with the BT heavy chain and then injected them with a dose of BT estimated to be the same as if the animals had inhaled large amounts of the toxin. The BT heavy chain protein did not appear to harm the mice, and it stimulated their immune systems to produce protective antibodies against the toxin.

Simpson's work has immediate clinical relevance in suggesting ways to manufacture a human vaccine against this potential bioterror weapon. Even better is that the vaccine might be able to be administered by inhalation, not injection. While an antitoxin to neutralize BT circulating in the bloodstream is available, quantities of this remedy are insufficient to rapidly treat large numbers of people. More importantly, an antitoxin cannot enter poisoned nerve cells, limiting the usefulness of such a strategy. A safe and effective inhalation vaccine could circumvent these problems.

[2] Fact sheet on botulinum toxin produced by the Center for Biosecurity at the University of Pittsburgh Medical Center (2003) http://www.upmc-biosecurity.org/pages/agents/botulism_facts.html

Promising Technologies

Making Microcircuits with Yeast Proteins

Sometimes serendipity, not necessity, can be the mother of invention. Case in point: the chance discovery of a new way to fabricate tiny electrical circuits from yeast proteins.

Susan Lindquist, Ph.D., a molecular biologist at the Whitehead Institute for Biomedical Research, is a leader in the study of prions. These misfolded forms of normal cellular proteins can cause serious illnesses, such as mad cow disease, in humans and animals. While studying prions in common brewer's yeast, she unexpectedly found one particular molecule called NM that can assemble itself into very thin fibers with surprising precision.

The prion fibers, which are quite similar to those found in the tangles within brains of people with Alzheimer's disease, turned out to have some rather unusual--and potentially quite useful--properties. The fibers are exceptionally durable and have very specific sizes, nanometers wide and up to several hundred micrometers long. The physical properties of the fibers suggest that they might be used to create extremely small "biotemplated" devices such as electric circuits.

Teaming with materials scientists, Lindquist and her collaborators then decided to see if they could genetically modify NM proteins to bind tiny particles of gold. The resulting gold-coated fibers formed stable electrical wires with ideal characteristics: very high conductivity and low resistance. In addition, the team found that NM proteins can be fused with other proteins, creating hybrid molecules that potentially could form complex circuits with special chemical and biological functions, such as those of enzymes. Lindquist speculates that this technology may lead to a wide variety of nanodevices with applications in both the electronics and medical industries.

Designing Protein Sensors

Unlike Sumo wrestlers--who can bind their opponents tightly using a number of moves and positions--proteins rely on the precise shape of their binding sites to attach to target molecules. Only through such specificity, for instance, can an antibody capture a virus. The ability of proteins to bind other molecules underlies innumerable life processes and medical treatments. For example, protein binding allows cell-to-cell communication, gives hormones their punch, and delivers chemotherapy to cancer cells.

Scientists study protein binding with the goal of finding ways to control it. An important step in this direction comes from computational biologist Homme Hellinga, Ph.D., of the Duke University Medical Center. His approach involves designing proteins that bind to new targets, which has potential applications across vast areas of medical science, toxic waste clean-up, and drug development.

Hellinga started with a known bacterial protein that binds to nutrients. He chose to modify this protein to bind molecules it would never encounter in nature, including the explosive TNT and

the brain chemical serotonin. Hellinga used a cluster of 20 linked computers to explore all of the ways atoms could be arranged in the protein's binding site--an astounding 10^{76} possibilities (that's more than a quadrillion multiplied by itself five times). With a sophisticated computer algorithm, he pared down these virtually countless possibilities to 17 promising arrangements that could be tested directly. Hellinga then constructed these 17 altered proteins in the laboratory. To determine the ability of the synthetic proteins to attach to their new targets, he engineered the proteins to glow when binding took place. The experiments lit up the lab. When inserted back into living bacteria, the designer proteins continued to carry out their new functions, taking the research closer to real-world applications.

The TNT-grabbing protein could serve as a biosensor to detect land mines or undetonated underwater explosives. Similar redesigned proteins could sniff out pollutants or chemical warfare agents. In addition, the ability to bind serotonin suggests possible diagnostic uses, since conditions such as depression and anxiety cause fluctuations in serotonin levels in the brain. The newly designed proteins could prove a boon to the pharmaceutical industry as well, since they can differentiate between mirror-image forms of molecular compounds. One form may be biologically active, while the other is inactive or even harmful. The ability to distinguish one from the other could lead to safer drugs in less time and at lower cost.

NIH Roadmap

NIGMS is highly involved in a number of NIH Roadmap activities related to the development of technology and resources that will accelerate the pace of basic biomedical research. This trans-NIH effort will benefit health by increasing the number of discoveries that can be translated into clinical applications.

Two roadmap initiatives will be particularly significant in advancing NIGMS' mission. One is the structural biology initiative, which focuses on producing large quantities of proteins found in biological membranes. These proteins, which include ion channel proteins like the one examined by 2003 Nobel laureate MacKinnon, are hard to produce and study but have such critical functions that they are prime targets for drug development.

The second initiative, bioinformatics and computational biology, addresses the pressing need in today's biomedical research for computational approaches--such as modeling--to extract meaning from massive amounts of data. Ideally, scientists would like to have easy access to an integrated biomedical computing environment. As a first step in building this resource, the roadmap initiative will create National Centers for Biomedical Computing. NIGMS is deeply committed to supporting these centers, which will develop a broad range of computational technologies and information tools for biomedical research. The centers will also help train new computational biologists and will collaborate with individual investigators on specific projects.

In addition to the initiatives discussed above, several roadmap activities in the New Pathways to Discovery category are closely related to NIGMS' mission areas. These are molecular libraries, probes for imaging dynamic processes in living cells, proteomics technology development, and nanomedicine. Initiatives in the Research Teams of the Future category tie into the Institute's

long-standing efforts to promote interdisciplinary research and training and to encourage high-risk research.

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 mounts 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

Knowing the structures of proteins helps us understand how they function in health and disease. The NIGMS Protein Structure Initiative will give scientists the ability to predict protein structures much more quickly, easily, and cheaply than is possible today. This knowledge will provide insights into the damage caused by misshapen proteins and aid in the development of new medicines.

The current, first phase of the Protein Structure Initiative supports pilot centers that are assembling a pipeline for rapid protein structure determination. The next phase, called the production phase, will begin in FY 2005. It will consist of several large, high-throughput centers that produce and determine the structures of many proteins as well as smaller centers that focus on challenging classes of proteins, such as membrane proteins and proteins from humans. Some of the smaller centers will also seek ways to overcome technological barriers to rapid, automated protein structure determination, while others will study proteins related to specific diseases.

Stem Cell Exploratory Centers

Human embryonic stem cells offer a unique way to ask basic questions about the biology of all cells. Scientists hope that stem cell research will shed light on--and possibly yield new ways to treat--many conditions, including Parkinson's disease, diabetes, spinal cord injury, heart disease, arthritis, vision and hearing loss, and wound healing.

Since research on human embryonic stem cells is still in its infancy, NIGMS has created programs to encourage scientists to use stem cells to explore fundamental biological processes. One of these programs establishes Exploratory Centers for Human Embryonic Stem Cell Research to improve understanding of the basic biology of stem cells and to promote the use of these cells as a model system for studying health and disease. Toward this end, the centers will train scientists to work with stem cells and develop new tools for studying the cells. The centers are required to use federally approved stem cell lines that are listed on the NIH Human Embryonic Stem Cell Registry.

NIGMS funded three exploratory centers in late FY 2003 at the University of Washington, Seattle/Fred Hutchinson Cancer Research Center, the University of Michigan Medical School,

and the WiCell Research Institute in Madison, Wisconsin. The Institute may fund additional centers in FY 2005.

Complex Biomedical Systems Research

NIGMS awarded two new grants in FY 2003 for Centers of Excellence in Complex Biomedical Systems Research. These centers are part of a larger effort to promote quantitative, interdisciplinary approaches to problems of biomedical significance, particularly those that involve the complex, interactive behavior of many components. Although the focus of each center is different, they all involve teams of biologists working with scientists in quantitative areas such as mathematics, physics, computer science, and engineering.

At the center based at Harvard University in Cambridge, Massachusetts, scientists will explore how collections of genes or proteins work together to carry out biological functions. The team will test the hypothesis that such collections behave as "modules" to perform specific functions essential to an organism's survival and reproduction.

The center at the Massachusetts Institute of Technology, which is also in Cambridge, will study "biological circuits" in human cells and tissues. By combining experiments with computer-based analysis and modeling of living systems, the researchers hope to predict how these circuits function under normal circumstances and how they go awry in disease.

The first two centers, which were funded in FY 2002, are at the University of Washington, Friday Harbor Laboratories, and Case Western Reserve University in Cleveland, Ohio.

Chemical Methodologies and Library Development

In recent years, chemists have learned to create high-quality collections of diverse chemical structures. These so-called chemical libraries are powerful tools for discovering potential new drugs and also for identifying molecules that scientists can use to probe biological processes. Because better methods are needed to realize the promise and utility of these libraries, NIGMS established Centers of Excellence in Chemical Methodologies in Library Development.

The Institute funded the first two of these centers in FY 2002, at Boston University and the University of Pittsburgh. In FY 2003, NIGMS funded two more centers, at the University of Kansas in Lawrence and Harvard Medical School. NIGMS expects that its investment in these centers will greatly expand the toolkit for a powerful experimental technique and pave the way for the development of new medicines.

Models of Infectious Disease Agent Study

NIGMS plans to fund the first pilot projects in its Models of Infectious Disease Agent Study (MIDAS) network in FY 2004. MIDAS, which is an integral component of the NIH biodefense plan, is designed to improve the nation's ability to respond to biological threats promptly and effectively. The network will develop computational tools and models of emerging infectious

diseases caused by naturally occurring or intentionally released agents. These tools and models will help policymakers, public health professionals, and researchers forecast, detect, control, and prevent new disease outbreaks.

"Glue" Grants

The newest NIGMS "glue" grant began in FY 2003 and focuses on the structure and function of lipids, which are fats and oils that have many essential functions in the cell. Imbalances in lipids cause or contribute to a wide range of ailments, including heart disease, arthritis, cancer, and Alzheimer's disease. A detailed understanding of lipids will improve understanding of their role in health and illness and will inform the development of new treatments. The lipid grant is led by scientists at the University of California, San Diego.

NIGMS funds four other glue grants, all of which bring together diverse groups of scientists to tackle biomedical research problems so large and complex that no single laboratory or small group of laboratories could take them on. These grants focus on communication within and between cells (one grant is led by the University of Texas Southwestern Medical Center at Dallas and another is led by The Scripps Research Institute), cell movement (led by the University of Virginia School of Medicine in Charlottesville), and the body's reaction to a burn or other traumatic injury (led by the Massachusetts General Hospital in Boston). NIGMS glue grants benefit the broader research community by generating and sharing data and research materials, as well as by serving as a testing ground for a new, highly collaborative approach to biomedical research.

Other Areas of Interest

Research Training

NIGMS continues to play a leading role in research training, supporting 45 percent of the predoctoral trainees and 28 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 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 underrepresented minority students and to report on the success of their efforts.

NIGMS trainees frequently contribute to major research advances. One example in FY 2003 came from basic research on proteins in the membrane that surrounds the cell's nucleus. The research team, which included an NIGMS postdoctoral fellow, discovered more than 50 previously unknown proteins and found that several of them are associated with rare, but

devastating, human muscle and nerve degeneration diseases. Knowing the proteins that may cause or contribute to these diseases is a first step toward finding ways to detect, prevent, or treat them.

The Institute has several long-standing research training programs that focus on areas in which there is a particularly serious need for well-prepared scientists. One of these programs, 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 2003, the MSTP supported 930 trainees.

Another special program, the Pharmacology Research Associate (PRAT) Program, is NIGMS' only intramural activity. PRAT fellows conduct 2 years of postdoctoral research in NIH or FDA laboratories, working in such cutting-edge areas as neurobiology, tumor biology, and cell signaling. In FY 2003, PRAT fellows published significant findings in areas ranging from cancer genetics to alcohol abuse.

Other NIGMS training programs advance the progress of science by preparing researchers to enter the fast-growing fields of biotechnology, bioinformatics, and computational biology. In addition, NIGMS will begin the creation of a new predoctoral training program in the area of biostatistics. The Institute held a workshop in December 2003 to explore the need for such a program. Because scientists trained in biostatistics contribute to many biomedical research areas, an NIGMS biostatistics training program will benefit other NIH institutes and centers.

In response to a September 2002 report by the National Research Council titled *Bio 2010: Undergraduate Education to Prepare Biomedical Research Scientists*, NIGMS is partnering with the NIH Office of Science Education on a program to transform undergraduate biology education. The report identified a critical need for educators to incorporate examples and perspectives from mathematics, physics, chemistry, computer science, and engineering into biology courses and lab experiments. The NIGMS/Office of Science Education program will develop and disseminate curriculum materials that can serve as models for the integration of the quantitative sciences into biology education.

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 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 FY 2003, one of the program's

grantees determined the structure of an antibody that is able to neutralize HIV. This work may offer a new approach for designing a vaccine against AIDS.

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 (MORE). 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 Branch

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 2003, MARC supported 649 undergraduate students at 53 institutions, 26 MARC predoctoral fellows, 3 faculty fellows, and 129 NIH predoctoral fellows.

In response to the growing need for quantitative approaches to biological problems, MARC funded two grants in FY 2003 to enable institutions with U*STAR programs to plan for introducing or integrating the quantitative sciences into their biology curricula. MARC may support additional planning grants in FY 2004, and it intends to fund the implementation of successful plans.

Minority Biomedical Research Support Branch

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).

The SCORE Program assists biomedical research faculty at minority-serving institutions in developing competitive research programs that increase the number of underrepresented minorities who are professionally engaged in biomedical research. The RISE Program 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. The IMSD encourages institutions with established research programs to initiate or expand activities to improve the academic and research capabilities of underrepresented minority students and to facilitate their progress toward careers in biomedical research.

In FY 2003, 838 faculty members at 117 institutions worked on 433 MBRS research projects. MBRS also supported 1,424 undergraduate and 736 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.

Special Initiatives

MORE supports several special initiatives that strive to develop new approaches for the recruitment and retention of minority biomedical scientists. One such activity is the Bridges to the Future Program, 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 inception of the Bridges Program in 1992, NIGMS has supported 150 programs, 9 of which received initial funding in FY 2003.

The division also supports two innovative awards to foster the development of new skills. The MORE Faculty Development Award enables eligible 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 in a research-intensive laboratory outside their home institutions. The Institutional Research and Academic Career Development Award (IRACDA) 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 on the Native American Research Centers for Health Program. 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. In FY 2003, the MORE Division announced plans 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.

Success Stories

In recognition of their exceptional achievements in nurturing minority students interested in research careers, three people associated with MORE programs were among the ten individuals who received 2003 Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring. They are R. David Bynum, Ph.D., of Stony Brook University, State University of New York; Sara L. Young of Montana State University-Bozeman; and Steven G. Greenbaum, Ph.D., of the City University of New York, Hunter College. Bynum directs a MARC program, Young runs an IMSD program, and Greenbaum is a SCORE grant investigator.

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

- LaVerne Ragster, Ph.D., a former MBRS program participant at San Diego State University, was inaugurated president of the University of the Virgin Islands in St. Thomas in March 2003. This marks the first time a former participant in one of the Institute's minority programs has become a university president.

- Brian Carr, Ph.D., a former MBRS program participant at the University of Southern Colorado in Pueblo, is now working as a research scientist at Merck & Co., Inc.

- Roberto Frontera-Suau, Ph.D., a former MARC program participant at the University of Puerto Rico, Medical Sciences Campus in San Juan and an IRACDA participant at the University of North Carolina at Chapel Hill, is now an assistant professor of biology at North Carolina's Elizabeth City State University.

- A research team led by MBRS-supported investigator Jorge Gardea-Torresdey, Ph.D., of the University of Texas at El Paso has shown that the mesquite tree can process a cancer-causing form of chromium into a non-toxic form of the metal. This work, which could lead to a new way to remove toxic chromium from industrial waste sites, has been praised by environmental groups and was selected by the journal that published it as "one of the best technological solutions of the year."

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.

Strategic Workforce Planning

The Institute has developed a strategic plan to help it manage its personnel resources effectively in a time of significant workforce restructuring. The plan addresses consolidation; competitive sourcing; career transition; succession planning, especially for mission-critical positions; and the use of various administrative authorities to aid in the outplacement of staff. In implementing the career transition component of the plan, NIGMS has sponsored workshops on change management and launched a comprehensive career transition services program. A key element of the plan is extensive communication with Institute employees to ensure that they are well-informed about NIGMS and NIH activities in the area of workforce restructuring.

Administrative Best Practices and Efficiencies

NIGMS continues to partner with the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke to share administrative best practices and collaborate on ways to achieve administrative efficiencies. In FY 2003, administrative leaders of the three institutes focused their discussions on risk management and succession planning.

A new electronic "checkbook" system developed by NIGMS staff is greatly improving efficiency in tracking budget obligations. The system automatically refreshes information as grants and contracts are funded and produces a variety of useful reports. This approach has proven so successful that three other NIH components have already adopted it.

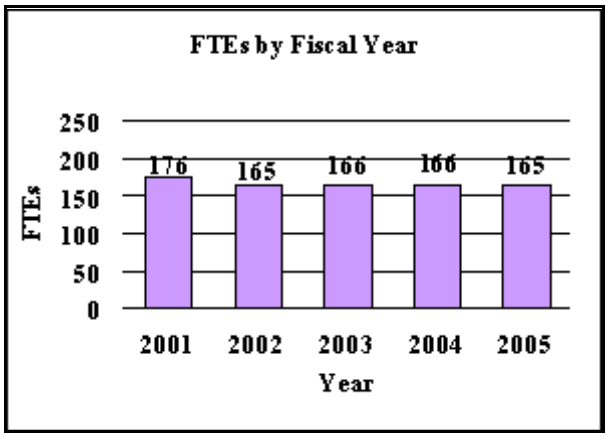
Electronic Research Administration

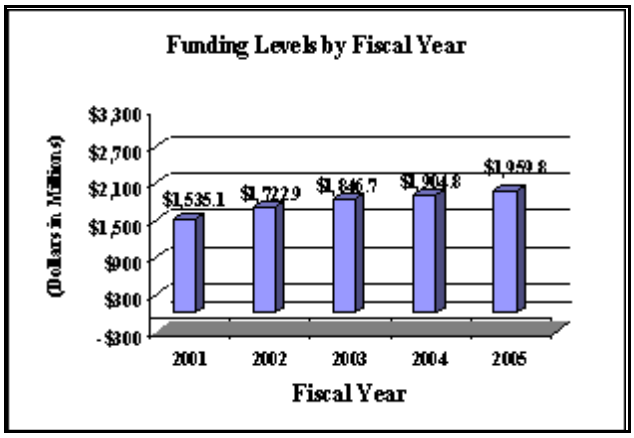
NIGMS is committed to using information technology to improve the efficiency of research administration. The Institute began receiving electronic progress reports from grantees in FY 2003, and NIGMS staff are participating in a pilot project on the electronic review of these progress reports. NIGMS has also moved more of its advisory council functions from paper to electronic form, saving reviewer and staff time as well as money previously spent to print and mail large amounts of material.

Budget Policy

The Fiscal Year 2005 budget request for the NIGMS is $1,959,810,000 an increase of $55,033,000 and 2.9 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NIGMS's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 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. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.



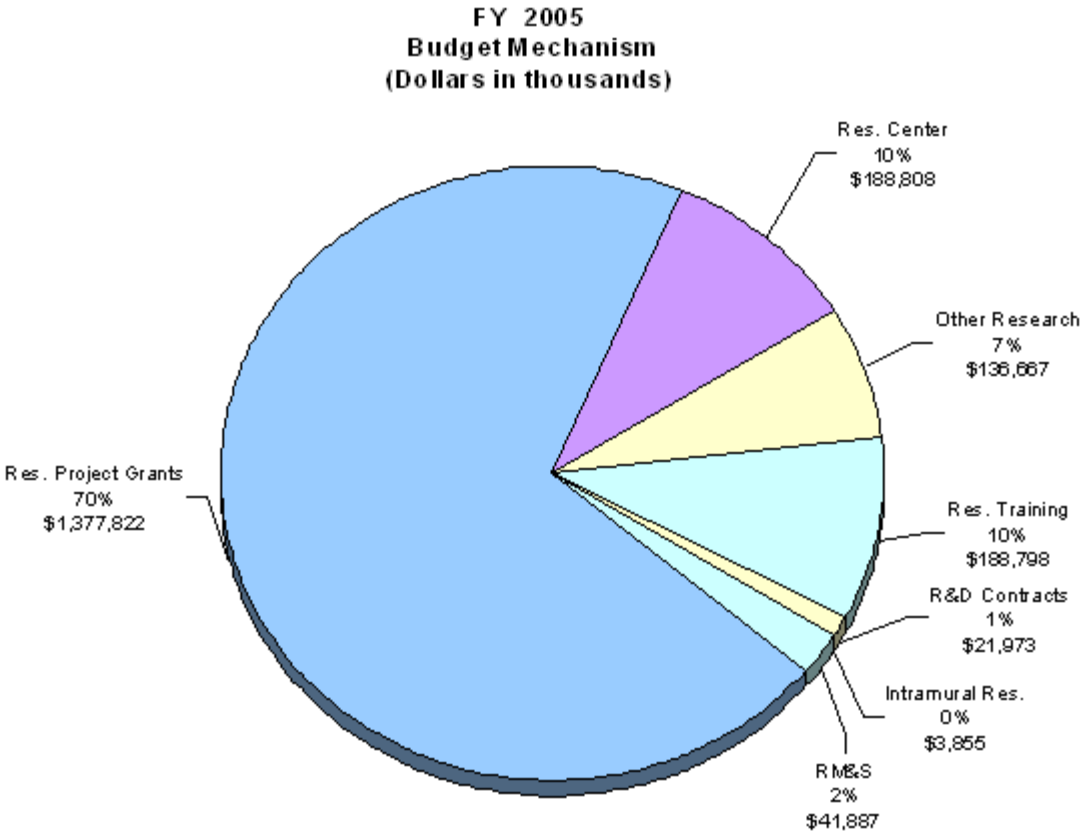


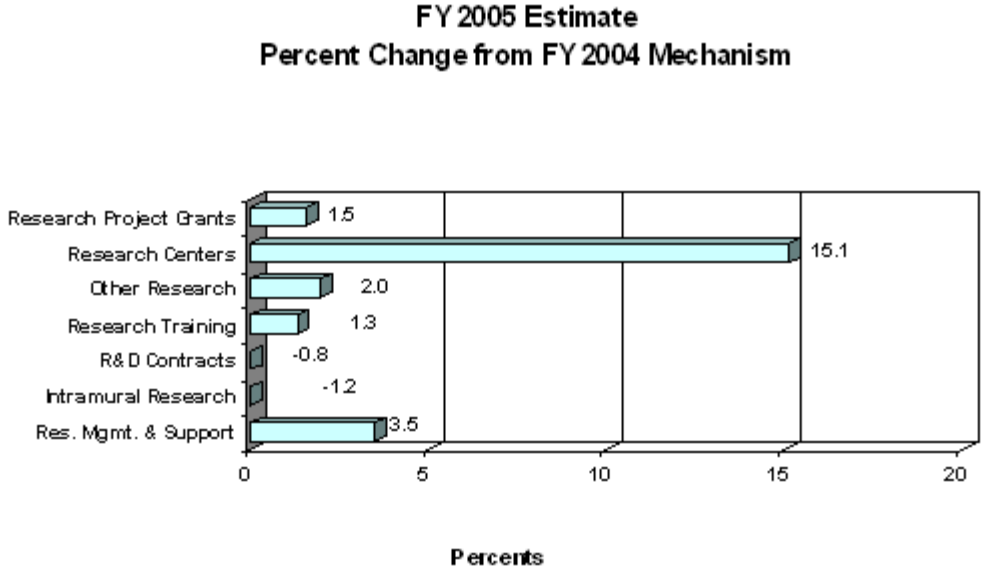
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. The NIGMS is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NIGMS will support 4,359 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 50 research centers, 310 other research grants, including 54 career awards, and 34 R&D contracts. Intramural Research received a decrease of 1% and Research Management and Support received an increase of 3.5% to support increased pay and estimated inflationary increases in FY 2005.

The Mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Mechanism - Total

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,900	$878,669,000	3,023	$974,289,000	2,985	$997,985,000
Administrative supplements	(277)	18,192,000	(277)	18,202,000	(278)	18,469,000
Full funded	57	7,865,000	57	7,944,000	57	8,023,000
Single year	1049	347,174,000	900	309,350,000	891	308,011,000
Renewal	589	208,007,000	530	196,950,000	527	196,678,000
New	452	138,107,000	362	111,274,000	356	110,202,000
Supplements	8	1,060,000	8	1,126,000	8	1,131,000
Subtotal, competing	1,106	355,039,000	957	317,294,000	948	316,034,000
Subtotal, RPGs	4,006	1,251,900,000	3,980	1,309,785,000	3,933	1,332,488,000
SBIR/STTR	137	40,943,000	148	44,083,000	152	45,334,000
Subtotal, RPGs	4,143	1,292,843,000	4,128	1,353,868,000	4,085	1,377,822,000
Research Centers:						
Specialized/comprehensive	47	140,595,000	48	160,755,000	49	185,135,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	17,057,000	1	2,815,000	1	3,241,000
Comparative medicine	0	807,000	0	432,000	0	432,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	47	158,459,000	49	164,002,000	50	188,808,000
Other Research:						
Research careers	42	9,651,000	46	10,672,000	54	11,305,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	37,000	0	46,000
Minority biomedical research support	154	99,130,000	154	102,104,000	154	103,125,000
Other	80	21,463,000	101	21,226,000	102	22,191,000
Subtotal, Other Research	276	130,244,000	301	134,039,000	310	136,667,000
Total Research Grants	4,466	1,581,546,000	4,478	1,651,909,000	4,445	1,703,297,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	552	21,243,000	552	21,934,000	552	22,071,000
Institutional awards	3,960	157,418,000	3,972	164,423,000	3,987	166,727,000
Total, Training	4,512	178,661,000	4,524	186,357,000	4,539	188,798,000
Research & development contracts	24	45,650,000	34	22,140,000	34	21,973,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	18	1,853,000	18	3,902,000	15	3,855,000
Research management and support	148	39,032,000	148	40,469,000	150	41,887,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIGMS	166	1,846,742,000	166	1,904,777,000	165	1,959,810,000
(RoadMap Support)		(0)		(6,540,000)		(12,340,000)
(Clinical Trials)		(0)		(0)		(0)

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National Institute of General Medical Sciences

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2003 Actual FTEs	FY 2003 Actual Amount	FY 2004 Final Conference FTEs	FY 2004 Final Conference Amount	FY 2005 Estimate FTEs	FY 2005 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Biomedical Research		$1,627,196		$1,674,049		$1,725,270		$51,221
Biomedical Research Training		178,661		186,357		188,798		2,441
Subtotal, Extramural research		1,805,857		1,860,406		1,914,068		53,662
Intramural Research	18	1,853	18	3,902	15	3,855	(3)	(47)
Res. Management & Support	148	39,032	148	40,469	150	41,887	2	1,418
Total	166	1,846,742	166	1,904,777	165	1,959,810	(1)	55,033

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Summary of Changes

FY 2004 Final Conference				$1,904,777,000
FY 2005 Estimated Budget Authority				1,959,810,000
Net change				55,033,000
	FY 2004 Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$1,378,000		$24,000
b. Annualization of January 2004 pay increase		1,378,000		14,000
c. January 2005 pay increase		1,378,000		16,000
d. One less day of pay		1,378,000		(5,000)
e. Payment for centrally furnished services		259,000		8,000
f. Increased cost of laboratory supplies, materials, and other expenses		2,265,000		31,000
Subtotal				88,000
2. Research Management and Support:				
a. Within grade increase		16,246,000		282,000
b. Annualization of January 2004 pay increase		16,246,000		167,000
c. January 2005 pay increase		16,246,000		183,000
d. One less day of pay		16,246,000		(62,000)
e. Payment for centrally furnished services		7,980,000		239,000
f. Increased cost of laboratory supplies, materials, and other expenses		16,243,000		449,000
Subtotal				1,258,000
Subtotal, Built-in				1,346,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Summary of Changes--continued

CHANGES	FY 2004 Budget Base No.	FY 2004 Budget Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,023	$992,491,000	(38)	$23,963,000
b. Competing	957	317,294,000	(9)	(1,260,000)
c. SBIR/STTR	148	44,083,000	4	1,251,000
Total	4,128	1,353,868,000	(43)	23,954,000
2. Research centers	49	164,002,000	1	24,806,000
3. Other research	301	134,039,000	9	2,628,000
4. Research training	4,524	186,357,000	15	2,441,000
5. Research and development contracts	34	22,140,000	0	(167,000)
Subtotal, extramural				53,662,000
	FTEs		FTEs	
6. Intramural research	18	3,902,000	(3)	(135,000)
7. Research management and support	148	40,469,000	2	160,000
Subtotal, program		1,904,777,000		53,687,000
Total changes	166		(1)	55,033,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Authority by Object

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	166	165	(1)
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$148,475	$151,700	$3,225
Average GM/GS grade	10.9	10.9	0.0
Average GM/GS salary	$72,214	$73,783	$1,569
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$0	$0	$0
Average salary of ungraded positions	103,557	105,806	2,249

OBJECT CLASSES		FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$8,183,000	$8,531,000	$348,000
11.3	Other than Full-Time Permanent	5,721,000	5,791,000	70,000
11.5	Other Personnel Compensation	425,000	444,000	19,000
11.7	Military Personnel	0	0	0
11.8	Special Personnel Services Payments	0	0	0
	Total, Personnel Compensation	14,329,000	14,766,000	437,000
12.1	Civilian Personnel Benefits	3,295,000	3,388,000	93,000
12.2	Military Personnel Benefits	0	0	0
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Costs	**17,624,000**	**18,154,000**	**530,000**
21.0	Travel & Transportation of Persons	470,000	482,000	12,000
22.0	Transportation of Things	22,000	23,000	1,000
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	13,000	13,000	0
23.3	Communications, Utilities & Miscellaneous Charges	158,000	162,000	4,000
24.0	Printing & Reproduction	502,000	514,000	12,000
25.1	Consulting Services	505,000	505,000	0
25.2	Other Services	4,970,000	5,091,000	121,000
25.3	Purchase of Goods & Services from Government Accounts	76,687,000	86,751,000	10,064,000
25.4	Operation & Maintenance of Facilities	34,000	35,000	1,000
25.5	Research & Development Contracts	1,969,000	2,039,000	70,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	202,000	207,000	5,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**84,367,000**	**94,628,000**	**10,261,000**
26.0	Supplies & Materials	290,000	297,000	7,000
31.0	Equipment	733,000	749,000	16,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,800,598,000	1,844,788,000	44,190,000
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	**1,887,153,000**	**1,941,656,000**	**54,503,000**
	Total Budget Authority by Object	**1,904,777,000**	**1,959,810,000**	**55,033,000**

NATIONAL INSTITUTES OF HEALTH
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Salaries and Expenses

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$8,183,000	$8,531,000	$348,000
Other Than Full-Time Permanent (11.3)	5,721,000	5,791,000	70,000
Other Personnel Compensation (11.5)	425,000	444,000	19,000
Military Personnel (11.7)	0	0	0
Special Personnel Services Payments (11.8)	0	0	0
Total Personnel Compensation (11.9)	**14,329,000**	**14,766,000**	**437,000**
Civilian Personnel Benefits (12.1)	3,295,000	3,388,000	93,000
Military Personnel Benefits (12.2)	0	0	0
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**17,624,000**	**18,154,000**	**530,000**
Travel (21.0)	470,000	482,000	12,000
Transportation of Things (22.0)	22,000	23,000	1,000
Rental Payments to Others (23.2)	13,000	13,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	158,000	162,000	4,000
Printing and Reproduction (24.0)	502,000	514,000	12,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	5,000	5,000	0
Other Services (25.2)	4,970,000	5,091,000	121,000
Purchases from Govt. Accounts (25.3)	12,143,000	19,365,000	7,222,000
Operation & Maintenance of Facilities (25.4)	34,000	35,000	1,000
Operation & Maintenance of Equipment (25.7)	202,000	207,000	5,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**17,354,000**	**24,703,000**	**7,349,000**
Supplies and Materials (26.0)	290,000	297,000	7,000
Subtotal, Non-Pay Costs	18,809,000	26,194,000	7,385,000
Total, Administrative Costs	**36,433,000**	**44,348,000**	**7,915,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORT

The following section represents FY 2004 Congressional requirements for reports and significant items derived from Senate Report 108-81. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2004 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

Minority Science Training Programs – The Committee continues to be pleased with the quality of NIGMS's training programs, particularly those that have a special focus on increasing the number of minority scientists such as the Minority Access to Research Careers [MARC] and Minority Biomedical Research Support [MBRS] programs. The Committee expects NIGMS to continue to support these important initiatives, and is particularly pleased that NIGMS has supported biomedical career opportunity programs for high school and undergraduate college students in conjunction with historically black health professions schools. The Committee urges continued, long-term support of this program. (p. 128)

Action taken or to be taken

NIGMS' Division of Minority Opportunities in Research (MORE) administers research and research training programs aimed at increasing the number of minority biomedical scientists. Specifically, the Minority Access to Research Careers (MARC) Branch offers a number of programs designed to encourage minority students to pursue training for scientific careers and the Minority Biomedical Research Support (MBRS) Branch aims to enhance the science curricula and research capabilities of faculty at institutions with substantial minority enrollments. Support for both of these important programs continues to be a priority for the Institute. In addition, NIGMS, in partnership with other NIH institutes, plans to continue to contribute funds in support of high school and undergraduate college students who are enrolled in biomedical research career opportunity programs in conjunction with historically black health professions institutions.

Item

Pharmacogenetics Research Network – The Committee commends NIGMS for its vision in creating the Pharmacogenetics Research Network to address the genetic bases for differences in patients' reactions to medications. Development of a deeper understanding of how genetics influences whether treatments work, don't work, or cause moderate or severe side effects is critical. This is an emerging field that will lead to a personalized approach to medicine. The Committee urges NIGMS to continue to develop and expand this field further with a strong emphasis on studying drug metabolism variation and treatment response in those disease states that affect large numbers of Americans, such as diabetes, mental illness and others. (p. 128)

Action taken or to be taken

NIGMS, and the other participating NIH institutes, plan to continue the Pharmacogenetics Research Network with a competition to be announced in FY2004, for funding in FY2005. The broad emphasis of this initiative will remain on collecting information on drug responses and making genotype-phenotype correlations. The network currently studies drug clearance pathways, including metabolism and transport, and disease applications, ranging from cardiovascular-pulmonary diseases to mental health disorders and cancers. The renewal competition will be an open one, thus allowing applications in these and other common disease areas. The network will also maintain its focus on PharmGKB, a public database for pharmacogenetics, which is intended as a tool for researchers and should enable the field by providing data, resources, and tools.

Item

Pre-Disease Pathways -- The Committee encourages the NIGMS to collaborate with other Institutes, including NCI and 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. 128)

Action taken or to be taken

NIGMS, in collaboration with other components of the NIH, such as the National Institute of Mental Health and the Office of Behavioral Social Sciences Research, will be 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 scheduled to convene in the spring of 2004 and plans to issue its recommendations in the form of a report in the fall of that year.

NATIONAL INSTITUTES OF HEALTH
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Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute of General Medical Sciences	Section 461	42§285b	Indefinite	$1,718,420,000	Indefinite	$1,771,012,000
National Research Service Awards	Section 487(d)	42§288	a/	186,357,000	b/	188,798,000
Total, Budget Authority				1,904,777,000		1,959,810,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
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Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1996	$907,674,000 2/	$946,971,000	$897,465,000 2/	$946,971,000
Rescission				(75,000)
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	1,917,033,000	1,916,333,000
Rescission				(11,495,000)
2005	1,959,810,000			

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
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Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	13	13	13
Office of Scientific Review	15	13	13
Office of Administrative Management	29	29	29
Division of Extramural Activities	41	39	39
Genetic and Developmental Biology Division	12	12	12
Pharmacology, Physiology, and Biological Chemistry Division	32	33	32
Cell Biology and Biophysics Division	16	17	17
Bioinformatics and Computational Biology Center	1	4	4
Minority Opportunities in Research Division	7	6	6
Total	166	166	165
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2001	10.7
2002	10.7
2003	10.9
2004	10.9
2005	10.9

NATIONAL INSTITUTES OF HEALTH
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Detail of Positions

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6			
ES-5			
ES-4	1	1	1
ES-3	1		
ES-2			
ES-1			
Subtotal	2	1	1
Total - ES Salary	$285,000	$148,475	$151,700
GM/GS-15	11	11	11
GM/GS-14	17	17	17
GM/GS-13	22	22	22
GS-12	11	11	11
GS-11	6	6	6
GS-10	1	1	1
GS-9	6	6	6
GS-8	14	13	13
GS-7	12	12	12
GS-6	5	5	5
GS-5	3	3	3
GS-4	2	2	2
GS-3	0	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	110	109	109
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	51	56	56
Total permanent positions	105	105	105
Total positions, end of year	163	163	162
Total full-time equivalent (FTE) employment,end of year	166	166	165
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$142,500	$148,475	$151,700
Average GM/GS grade	10.9	10.9	10.9
Average GM/GS salary	$69,308	$72,214	$73,783