DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

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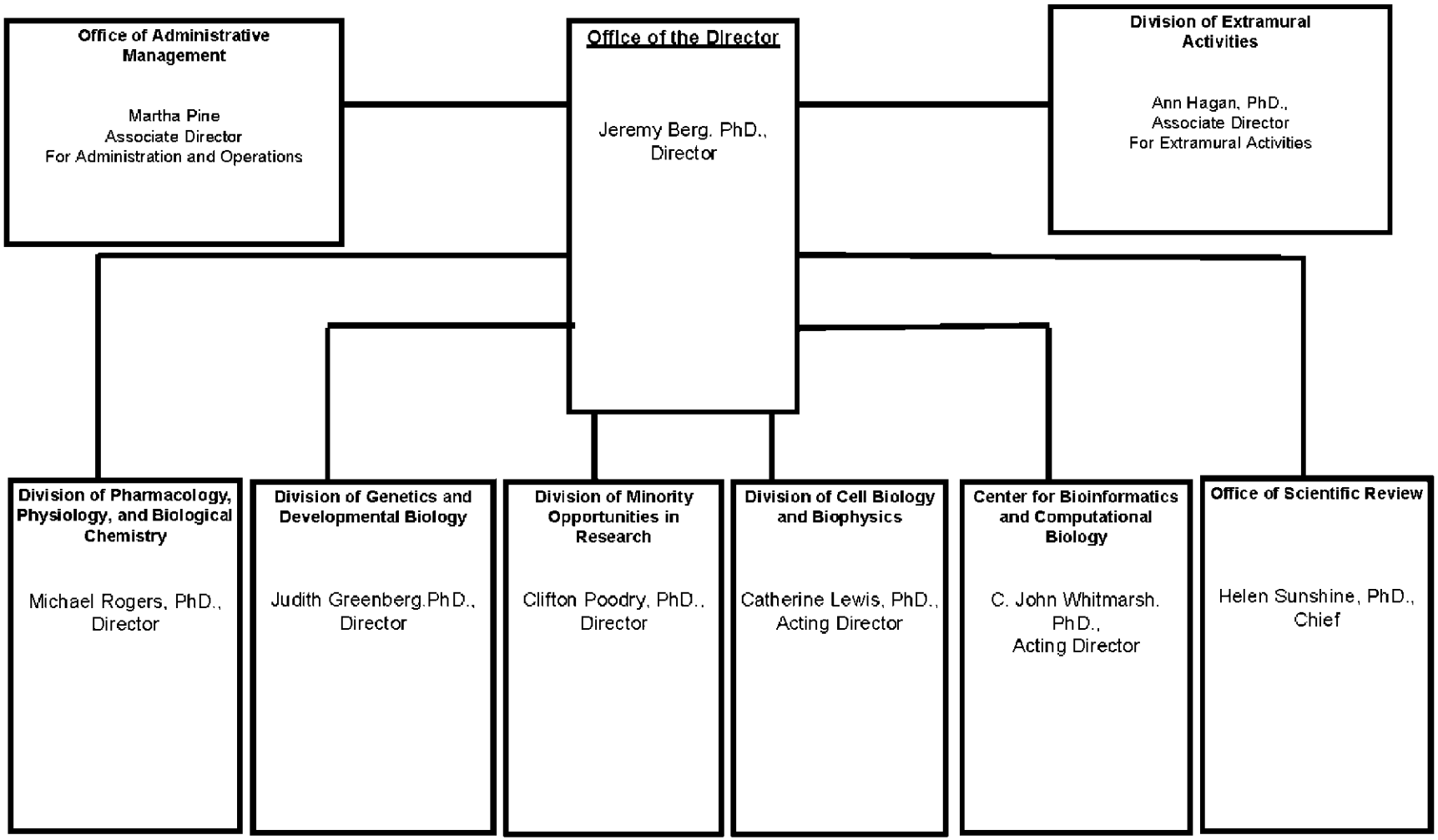
Organization Structure



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, [$1,955,170,000] $*1,923,481,000*.

[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2006, as enacted by Public Law (109-149)]

National Institutes of Health
National Institute General Medical Sciences

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$1,959,810,000	$1,955,170,000	$1,923,481,000
Enacted Rescissions	(15,743,000)	(19,552,000)	0
Subtotal, Adjusted Appropriation	1,944,067,000	1,935,618,000	1,923,481,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(12,290,000)	(17,297,000)	0
Comparative transfer from OD for NIH Roadmap	12,290,000	17,297,000	0
Subtotal, adjusted budget authority	1,944,067,000	1,935,618,000	1,923,481,000
Unobligated Balance, start of year	0	0	0
Revenue from Breast Cancer Stamp 2/	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,944,067,000	1,935,618,000	1,923,481,000
Unobligated balance lapsing	(87,000)	0	0
Total obligations	1,943,980,000	1,935,618,000	1,923,481,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $1,475,000 FY 2006 - $7,000,000 FY 2007 - $7,000,000

Justification
National Institute of General Medical Sciences

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

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
128	$1,944,067,000	134	$1,935,618,000	135	$1,923,481,000	1	($12,137,000)

This document provides justification for the Fiscal Year 2007 research activities of the National Institute of General Medical Sciences (NIGMS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

Introduction

NIGMS makes strategic investments in fields of science and in scientists, whose creativity and independent findings often coalesce into major research advances. A case in point is the recent discovery by a number of Institute grantees that microRNAs, a newly identified type of genetic material, play a central role in controlling gene activity. The insight was paradigm-shifting because scientists previously thought that only proteins could do this job. By also revealing that microRNAs are key to cancer and stem-cell growth, the research offers a new target for the development of medicines and other treatments.

The tremendous value of long-term NIGMS investments is evident in the 2005 Nobel Prize in chemistry, as well. The Institute has provided decades of support to two of the three chemists who won the prize: Robert Grubbs, Ph.D., of the California Institute of Technology in Pasadena and Richard Schrock, Ph.D., of the Massachusetts Institute of Technology in Cambridge. They were honored for developing important chemical catalysts that have a wealth of pharmaceutical and other industrial uses.

In addition to supporting individuals, NIGMS has been ahead of the curve in recruiting able and diverse teams of researchers to tackle difficult problems that require a multidisciplinary approach from the start. Many in the scientific community have embraced the Institute's "glue grant" program, launched 5 years ago to promote collaborations across traditional academic and disciplinary boundaries. An example of the success of this program is the recent identification of a genetic signature that is a first step toward predicting how a severely injured patient will fare in response to treatment.

Another highly promising NIGMS team science approach is the Models of Infectious Disease Agent Study (MIDAS) program, which draws on the expertise of mathematicians, computer scientists, biologists, social scientists, and others to model infectious disease outbreaks. Although MIDAS scientists are still in the early stages of crafting tools and gathering underlying data, their work is already providing guidance for policy development in preparation for public health emergencies.

More complete descriptions 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: Pharmacogenetics Research Leads the Way to Individualized Therapy

Medicines that work wonders for some can be ineffective—or even toxic—to others. Why? A person`s age, weight, lifestyle. and other medicines play a role. but genes also have an important influence. The study of how genes affect drug responses is called pharmacogenetics. The goal of this research is to enable doctors to move beyond the current, one-size-fits-all approach to treatment and toward prescribing the drugs and dosages that will work best for each person.

Birth of a Field

As early as the 1930s, scientists began to realize that natural genetic variations could cause people to respond differently to medicines. Sometimes, these differences can have life-and-death ramifications. For example, the standard, usually effective dose of a drug to treat childhood leukemia can be a fatal overdose or a useless underdose in certain rare individuals.

In the 1950s, scientists started to nail down which genes were responsible for these differences. In 1957, a researcher officially launched the field of pharmacogenetics by publishing a paper that described four early examples, including wide-ranging differences in people's responses to an antimalarial drug (primaquine) and a muscle relaxant used in surgery (succinylcholine). The term "pharmacogenetics" was coined 2 years later.

In 1967, the New York Academy of Sciences hosted the first international conference on pharmacogenetics, bringing together investigators studying the ever-growing number of exaggerated, unexpected, or ineffective drug responses seen in some people and thought to be due to genetic diversity. Throughout the 1980s, more than 100 other examples were added to the list.

A Strong Foundation

The genetic variations relevant to pharmacogenetics occur in molecules that drugs interact with as they enter, move through. and exit the body. Since its inception in 1962, NIGMS has funded basic studies of the biochemistry. structure, function, and action of these molecules, providing a strong foundation for pharmacogenetics research. In 1982, NIGMS grantee Richard M. Weinshilboum, M.D., of the Mayo Clinic College of Medicine in Rochester. Minnesota, characterized the gene, called TPMT, that is responsible for the different effects of the antileukemia drug mentioned above. This provided one of the first biochemical explanations for varying drug responses. Now, a simple blood test given to children beginning chemotherapy can indicate the appropriate dose of the medicine for each child.

Many pharmacogenetic studies focus on cytochromes P450, a large family of enzymes that metabolize, or break down, medicines. Scientists now recognize more than 20 forms of P450, each of which can have dozens of variants. NIGMS grantee David A. Flockhart, M.D., Ph.D., of the Indiana University School of Medicine in Indianapolis maintains an online list of about 250 drugs and other substances whose activities are determined by P450 enzymes (http://medicine.iupui.edu/flockhart/).

The most abundant P450 enzyme found in the liver and intestines is CYP3A, which metabolizes more than half of all drugs. NIGMS-supported scientists have contributed significantly to the understanding of CYP3A and continue to study the molecular details of the enzyme, analyze the prevalence of different gene variants, and correlate these variants with how well people metabolize medicines.

Capitalizing on Opportunities

The Human Genome Project gave scientists access to the sequence of all human genes, opening up new research avenues in pharmacogenetics and other fields. A number of prominent scientists predict that testing of patients for known pharmacogenetic variants will be one of the first clinical applications of genomics.

Recognizing that the time was right for an organized, large-scale effort in pharmacogenetics, NIGMS, in partnership with other NIH components, established the NIH Pharmacogenetics Research Network (http://www.nigms.nih.gov/pharmacogenetics) in 2000. The researchers and physicians in this nationwide collaboration share their data in a knowledge base available to all scientists (http://www.pharmgkb.org/). In the network's first 5 years, its scientists focused on the molecular targets of drugs and the enzymes and "gatekeeper" molecules that remove drugs from the body. They made nearly 400 discoveries, including those described below.

- **Genes Influence Response to Breast Cancer Treatment**—Individuals with a specific genetic variation in the drug-metabolizing enzyme CYP2D6 do not respond well to tamoxifen, a widely prescribed treatment for breast cancer. On average, breast cancer survivors with the genetic variation live disease-free for only 4 years after treatment, whereas those without the variation average 11 years. This discovery, by the Flockhart research team, may lead to greater use of genetic tests to identify those women who are most likely to benefit from tamoxifen.

- **Better Blood Thinning**—Every year in the United States, 2 million orthopedic surgery and cardiac patients take warfarin (Coumadin®) to prevent blood clotting. Finding the correct dose is notoriously difficult, and the wrong dose can have life-threatening consequences. Too much causes excessive bleeding and too little could lead to deadly blood clots. Researchers led by Allan E. Rettie, Ph.D., of the University of Washington in Seattle found that differences in a single gene, VKORC1, influence the dose of the drug that is most effective for each person. This discovery is expected to enable faster and more precise warfarin dosing.

- **Gene Tests to Guide Asthma Treatment**—A research team led by Scott T. Weiss, M.D., of Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts, discovered that genetic variations in certain sets of genes, including those called CRHR1 and ADRB2, affect the way people respond to asthma medicines (inhaled steroids and beta agonists). To help doctors use this discovery to guide treatment decisions, the research team is now developing prototype tests for the gene variants.

In September 2005, NIGMS renewed the Pharmacogenetics Research Network and Knowledge Base, promising a steady stream of advances during the next 5 years. NIGMS also takes seriously the ethical, legal, and social implications of the use of pharmacogenetic information and seeks to support research in these areas.

Together with a number of other NIH components, NIGMS is supporting the International HapMap Project (http://www.hapmap.org/), a worldwide collaboration of scientists that is developing a map of all the common variations in the human genome. The HapMap is already helping researchers find genes affecting health, disease, and drug responses.

Future Promise

As scientists gain a better understanding of the genes involved in different drug responses and develop tests for relevant gene variants, pharmacogenetics will steadily move from the bench to the bedside. Commercial tests are already available for several enzymes whose variations result in different drug responses, including two members of the P450 family (CYP2D6 and CYP2D9) and TPMT.

The U.S. Food and Drug Administration has begun to incorporate pharmacogenetic considerations in the prescribing information for some drugs. For example, in response to NIGMS-supported research led by Mark J. Ratain, M.D., of the University of Chicago, the label of an anticancer drug called irinotecan was changed in the summer of 2005. The new label encourages doctors to use a lower starting dose for patients known to have a genetic variation that increases their risk for life-threatening reactions to the drug.

In the future, pharmacogenetics researchers hope not only to predict and adjust for drug effects caused by single genes, but to do the same in treating more complex conditions like high blood pressure and diabetes that result from a combination of genes. The ultimate goal is for doctors to prescribe to all of their patients the right dose of the right medication the first time. This is echoed by HHS Secretary Michael O. Leavitt in his 500-Day Plan (http://www.hhs.gov/500DayPlan/500dayplan.html), in which he envisions "a nation in which. . .medications are safer and more effective because they are chosen based on the patient's personal characteristics."

Science Advances

These science advances convey the breadth and significance of NIGMS-supported research in such areas as cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics, and computational biology. Although only the lead scientists are named, coworkers and collaborators contributed substantially to the achievements.

Understanding Life Processes

MicroRNAs Debut as Key Actors in Health and Disease

One of the dogmas of biology has been that proteins, the cellular workhorses of our bodies, perform the critical job of controlling gene activity. But a series of recent discoveries is painting a strikingly different picture.

A newly identified kind of RNA, called microRNA for its tiny size, appears to control a third of our genes. Scientists are finding that microRNAs play starring roles in a remarkably wide range of biological processes.

Two studies in 2005 implicate microRNAs in cancer. Using microscopic roundworms, Frank Slack, Ph.D., of Yale University in New Haven, Connecticut, discovered that one particular microRNA can quiet Ras, a protein known to be central to tumor formation when it is mutated. In a separate study, Gregory Hannon, Ph.D., of Cold Spring Harbor Laboratory in New York identified other microRNAs linked to the severity of B-cell lymphoma in mice. These findings open promising new avenues for preventing, diagnosing, and treating cancer.

In a third study, Richard Carthew, Ph.D., of Northwestern University in Evanston, Illinois, and Hannele Ruohola-Baker, Ph.D., of the University of Washington in Seattle uncovered telltale signs of microRNA involvement in stem cell growth. Unlike most cells, stem cells have the ability to continuously renew themselves, yet scientists do not understand how this happens. The new research, done in fruit flies, revealed that stem cells need certain microRNAs to maintain their ability to divide endlessly.

Research on microRNA is still in the early stages, but the recent discoveries linking microRNAs with cancer and stem cell biology are fueling excitement about the potential therapeutic uses of these multitalented molecules.

Human Growth Factors Maintain Stem Cells' Clean Slate

Human embryonic stem cells (hESCs) have the remarkable ability to turn into any type of cell in the body. For this reason, these cells give basic researchers an ideal model for studying early human development and advancing regenerative medicine. Typically, scientists grow hESCs in the laboratory by culturing them on a layer of mouse cells that prevents the hESCs from changing into other cell types too soon. Although stem cell therapy is still years away, scientists have searched for a way to get rid of this step because it poses a risk of contamination from animal cells.

New results from two basic researchers working independently may solve this problem. One of the two researchers who originally discovered hESCs, James Thomson, V.M.D., Ph.D., of the WiCell Research Institute in Madison, Wisconsin, discovered that adding a human protein, basic fibroblast growth factor, to a stripped-down version of cell-culture broth kept the hESCs in an undifferentiated state. It did this, he found, by stopping molecular signals that provoke the cells to mature into other cell types. Thomson also learned that by using his method, mouse cells were no longer needed. In related work, Ali Hemmati-Brivanlou, Ph.D., of the Rockefeller University in New York City discovered that turning on the production of yet another human growth factor also helped to maintain the human stem cells' clean slate and did not require mouse cells either.

The findings are a critical step forward in the quest to understand the basic biology of hESCs. What's more, by simplifying the procedure for growing hESCs in the absence of animal cells, the researchers pave the way for future scientists aiming to develop stem-cell therapies to replace diseased or injured cells.

Cell Death Discovery Has Healing Power

Decades of research have taught scientists that cells have two ways to die. The first, necrosis, is a nonspecific response to an overwhelming stress such as a heart attack or exposure to poison. Researchers have viewed the other kind of cell death, known as apoptosis, as a normal, programmed process that helps shape organs and rid the body of potentially harmful or unneeded cells. Recently, however, scientists have begun to suspect that apoptosis may also have a dark side, potentially contributing to neurodegenerative diseases such as Alzheimer's and Parkinson's.

New work from Junying Yuan, Ph.D., of Harvard Medical School may help settle the issue by defining a third way cells can perish. Necroptosis, as the name suggests, shares characteristics with both necrosis and apoptosis, and Yuan has found that it can occur in healthy cells. Under the microscope, a cell dying by necroptosis looks a lot like a cell dying by necrosis—it swells up and bursts, spewing its contents on neighboring cells. However, as a cell dies this way, it proceeds through a series of chemical steps resembling apoptosis. Yuan found that necroptosis contributed to delayed brain injury in mice suffering a stroke-like event. In further work, she identified a molecule, necrostatin-1, that significantly lessened necroptosis-induced brain damage.

Yuan's research highlights the value of exploring basic cellular function to uncover new knowledge about health and disease. The findings may also help scientists learn how to develop necrostatin-1 or similar molecules as medicines for stroke or other medical conditions that involve necroptosis.

Basic Studies Illuminate Disease Mechanisms

Genes Could Help Predict Trauma Outcome

Each year, doctors treat millions of trauma victims without being able to predict how each person is likely to fare. Even people with nearly identical injuries can have dramatically different outcomes, with some inexplicably developing life-threatening complications like multiple organ failure or body-wide inflammation.

Thanks to an NIGMS "glue grant" that brought clinicians and basic researchers together to attack this problem, doctors are one step closer to knowing how best to treat trauma patients. A multidisciplinary group of scientists led by trauma surgeon J. Perren Cobb, M.D., of the Washington University School of Medicine in St. Louis, Missouri, scanned genetic material from trauma patients and healthy volunteers. The researchers were looking for differences in gene activity that might be associated with the most deadly effects of severe trauma. They found that, compared to healthy people, the trauma patients' white blood cells showed dramatic differences in the activity of certain genes. Because white blood cells are involved in inflammation, these results shed light on inflammation's role in injury response.

This study is one of the first to standardize "gene chip" experiments across several medical centers and show that such a genetic test can give informative results in a clinical setting. The work is an early, but significant, step toward the researchers' goal of using genetic information to guide trauma treatment.

RNA Cut-and-Paste Makes an Adult Heart

Much like we mix and match shirts, pants, and shoes to put together different outfits, a cell can shuffle segments of its genetic material to produce thousands of different, but related, proteins. This process, called alternative splicing, acts on RNA molecules that carry information from DNA to the cell's protein-making machinery. In many cases, cells use alternative splicing to

make particular proteins according to the circumstances: Just as you might choose to wear a raincoat on a soggy day, a cell can make a protein variant to suit its needs.

Now, basic researchers have discovered that alternative splicing appears to play a key role in the development of a healthy heart. Xiang-Dong Fu, Ph.D., of the University of California, San Diego, used genetic engineering technology to create mice that could not produce ASF/SF2, a protein known to be involved in cutting and pasting RNA. Although these experimental mice looked normal at birth, within a few weeks their hearts could not pump blood very well and they died soon thereafter. Fu discovered that, without the proper ASF/SF2 splicing tool, the mice made the wrong version of an important heart enzyme that helps transform a juvenile mouse heart into that of an adult. The enzyme, the scientists learned, has also been linked to heart attacks.

Fu's findings may lead to a deeper understanding of alternative splicing in the normal development of body organs. The research may also shed light on why heart attacks occur and could suggest strategies to prevent them.

New Approaches to Therapeutics

Scientists Find New Ways to Resist Resistance

When scientists discovered penicillin's antibacterial properties in the early 20th century, medicine was transformed. But just a few years after people began using this drug, penicillin-resistant bacteria started to appear. Today, antibiotic resistance remains a public health challenge, making it increasingly hard to treat tuberculosis, pneumonia, and many other infections. Scientists continue to struggle to develop a fail-safe plan, but in 2005, basic researchers made progress on two fronts.

First, using a hardy microorganism isolated from the Dead Sea, Thomas Steitz, Ph.D., and Peter Moore, Ph.D., both of Yale University, determined the protein structures of drug-resistant and drug-sensitive bacterial ribosomes physically attached to different antibiotics. This strategy is revealing because many antibiotics kill bacteria by binding to the RNA components of their protein-making ribosomes. The new structures show why a single genetic change prevents many antibiotics from tightly gripping onto ribosomes and explains why these versions can only weakly block bacterial protein production. Researchers at a biotechnology start-up company that Steitz and Moore helped to establish are using this structural information to develop new antibiotics.

In the other study, Marcus W. Feldman, Ph.D., of Stanford University in California investigated the role humans play in spreading antibiotic resistance. He created a simple mathematical model comparing people who tend to seek medical treatment with those who generally avoid taking medicines, including antibiotics. The model suggested that when people avoid antibiotics, resistance does not develop. But when people do take these drugs, resistant bacteria quickly gain footing and may even flourish as the antibiotic-sensitive bacteria die off. Feldman's findings point to an important link between patterns of antibiotic use and the emergence of drug-resistant bacteria.

Although these studies were widely different in scope, they both suggest new research directions for battling the increasingly urgent problem of antibiotic resistance.

Brain's Fear Center Affects Memory During Anesthesia

Despite the fact that general anesthetics have been used since the 1800s, scientists still do not have a thorough understanding of how these powerful drugs work in the brain. In addition to relieving pain and causing loss of consciousness, anesthetics are known to induce amnesia during the surgical period. A recent study has shed light on this aspect of anesthetic action.

Using rats as a research model, Michael T. Alkire, M.D., of the University of California, Irvine, has uncovered the role of the amygdala—a brain region involved in fear, anxiety, and emotion—in memory loss caused by the anesthetic sevoflurane. He placed two groups of rats, one mildly anesthetized and the other untreated, in a lighted chamber facing a dark tunnel. If the rats entered the dark area, an environment rodents prefer, Alkire gave them a brief electrical shock.

The unanesthetized animals remembered this shock until the next day and quickly learned to stay in the safer, lighted environment. However, those treated with sevoflurane behaved differently: Unable to remember the bad experience, these animals continued to enter the tunnel and receive a shock. When Alkire incapacitated the amygdalas of the anesthetized rats, he observed that they could then remember, and avoid, the shock. He concluded that sevoflurane could erase a rat's memory during the training session, but only if the rodent's amygdala was working properly.

By pinpointing the amygdala's role in memory function during anesthesia, this research adds to the growing body of knowledge about how anesthetics exert their effects. It has particular relevance to the relatively rare situations in which patients experience episodes of awareness—and sometimes also pain—during anesthesia, but are unable to move or report the problem. In some people, the experience can trigger post-traumatic stress disorder. A better understanding of how anesthetics interact with the brain to cause amnesia could help reduce or eliminate episodes of awareness. The study also provides new insights into memory formation, especially those related to unpleasant or emotional events.

Promising Technologies

State-of-the-Art Sensors Find Traces of Zinc and Mercury

Metals in the body keep us healthy, but they can also make us sick. While small amounts of iron, copper, and zinc help proteins carry out their regular functions, metals in the wrong amount or the wrong place can cause trouble. Recent research implicates zinc in the development of Alzheimer's and Parkinson's diseases as well as strokes, seizures, and head injuries. Exposure to mercury, which is harmful in any amount because the body can't get rid of it, can also cause neurological damage. Techniques that reliably locate small amounts of metals in the body are key to understanding the progression and treatment of these brain disorders as well as the roles that metals play in normal processes. Some detection methods currently exist, but most are either imprecise or difficult to implement.

Stephen Lippard, Ph.D., of the Massachusetts Institute of Technology in Cambridge may have a new way. He has developed sensors that reveal tiny amounts of zinc and mercury in cells, tissues, or water. When Lippard applied these chemical sensors to biological samples and then shone light on them, molecules of zinc or mercury in the samples lit up. Lippard tested the zinc sensors on brain tissue from rodents with head trauma or seizures and found that the sensors precisely identified zinc in damaged nerve cells. Lippard has also fashioned a sensor that selectively pinpoints even low levels of mercury in water.

The fluorescent chemosensors may offer new tools for imaging metals in the body and for studying the role of these molecules in health and disease. The technology may also prove useful for monitoring environmental quality in water, soil, and elsewhere.

Supports HHS Goal 2, Objective 2.2: Improve the safety of food, drugs, biological products, and medical devices

Chicken Eggs Offer Better Way to Produce Important Drugs

In recent years, a new class of drugs called monoclonal antibodies has become an important treatment for cancer and other illnesses. Therapeutic monoclonal antibodies, such as the breast cancer therapy Herceptin®, work the same way natural antibodies work: They identify and attach to receptors on cell surfaces to block unhealthy molecular interactions or to alert other cells in the immune system to launch an attack. Currently, monoclonal antibody drugs are manufactured by inserting the genes encoding these proteins into cultured animal cells. But the high cost of installing and operating cell-culture production facilities has prompted scientists to look for a better method.

With funding from a small business innovation grant, Lei Zhu of Origen Therapeutics in Burlingame, California, figured out how to make monoclonal antibody drugs in chicken eggs. She and her coworkers inserted genetic instructions into the chicken genome, directing the production of antibodies in egg whites. Extracting the protein drugs was straightforward and efficient, and laboratory tests showed that the antibodies were even more effective at killing cancer cells than were antibodies made by traditional means.

This work is a technical milestone that could ease the development of other therapeutic antibodies. In addition to the 17 approved antibodies currently marketed as medicines to treat cancer, arthritis, multiple sclerosis, and inflammatory bowel disease, dozens more are currently in the development pipeline. Streamlined approaches to make therapeutic monoclonal antibodies efficiently and economically may mean less expensive—and potentially more effective—medicines in the not-too-distant future.

Supports HHS Goal 4, Objective 4.2: Accelerate private sector development of new drugs, biologic therapies, and medical technology

Computer Models Simulate Flu Epidemic, Could Guide Response

When a type of flu found in poultry and other fowl started infecting people in Southeast Asia, scientists and policymakers around the world began to worry. By the fall of 2005, more than 100 cases of avian, or "bird," flu had been documented in humans and about half of these had

resulted in death. Researchers are concerned that bird flu could provoke a worldwide outbreak. Because most people have no prior immunity to this flu virus strain, a bird flu pandemic could potentially kill millions.

Early progress in preparing for a possible outbreak emerges from scientists involved in the Models of Infectious Disease Agent Study, a research network designing simulations of disease spread with the goal of identifying effective control strategies.

A multidisciplinary team including Neil M. Ferguson, D.Phil., of Imperial College in London and Ira Longini, Ph.D., of Emory University in Atlanta, Georgia, used computer models to simulate a human outbreak of avian flu in Southeast Asia and to test what intervention measures could contain it. The models were based on extensive population data from Thailand and information about past flu outbreaks. As the first hypothetical cases showed up in each modeling scenario, the researchers introduced various intervention strategies, such as giving antiviral drugs, vaccinating before an outbreak, quarantining, or a combination of these methods. The models differed in many ways, but each suggested that a carefully chosen combination of public health measures along with the quick implementation and large-scale use of antiviral drugs could stop the spread of an avian flu outbreak at its source.

As the researchers continue to refine and test their models, they are also developing preliminary models for the United States. Although the simulations are still in progress, the MIDAS models offer new knowledge that scientists and policymakers are considering as they prepare for a possible outbreak.

Supports HHS Goal 2, Objective 2.1: Build the capacity of the health care system to respond to public health threats in a more timely and effective manner, especially bioterrorism threats

NIH Roadmap

NIGMS plays a significant role in a number of activities within the NIH Roadmap for Medical Research. It leads the Bioinformatics and Computational Biology and the Structural Biology initiatives. The Institute is also responsible for major components of the Molecular Libraries and Imaging and the Interdisciplinary Research initiatives. FY 2005 funding through these elements of the NIH Roadmap launched efforts to:

- Accelerate creation of the core of a wide-ranging computing infrastructure that is urgently needed for rapid progress in biomedical research. Three new National Centers for Biomedical Computing joined four others funded in FY 2004 to develop 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.

- Develop innovative methods for speeding the determination of membrane protein structures. Membrane proteins control the movement of molecules into and out of cells, making them key players in such critical functions as nerve impulses and immune response. Importantly, these proteins are the targets for a large number of therapeutic drugs. The new grants include

several exploratory projects that are considered scientifically risky but that, if successful, promise to have a high impact on the field.

- Devise new methods for discovering, deriving, and producing biologically active compounds from natural sources such as microorganisms, marine organisms, and plants. The goal is to exploit nature's prolific supply of molecules with therapeutic potential.

- Generate collections of diverse chemical compounds that will be screened to identify molecules capable of enhancing or inhibiting specific biological functions. Such molecules have many applications in research and could aid in the discovery of new drugs.

- Improve ways of predicting the possible toxicity of compounds much earlier in the drug development process.

- Build exquisitely sensitive imaging tools to track individual molecules and pathways in living cells in order to understand their roles in health and disease.

Also in FY 2005, NIGMS became the administrative home for the NIH Director's Pioneer Award program. This award complements NIH's traditional, investigator-initiated grant programs by supporting exceptionally creative scientists who take innovative approaches to major challenges in biomedical research. Recipients gain the intellectual freedom to pursue groundbreaking new research directions that have the potential for unusually great impact.

The 13 Pioneer awardees selected in FY 2005 work in diverse areas, including neuroscience, genetics, epidemiology, chemistry, stem cell biology, behavioral science, infectious diseases, and technology development. Six are women, one is from an underrepresented minority group, and more than half are at relatively early stages of their careers (the associate professor level or below).

NIGMS benefits greatly from these and other NIH Roadmap initiatives, which complement and advance the Institute's own efforts in bioinformatics and computational biology, structural biology, chemistry, pharmacology, and molecular imaging. The high degree of trans-NIH collaboration in Roadmap activities makes it possible to embark on projects that are larger in scale, require a broader range of expertise, and entail higher risk than NIGMS or any other institute could realistically take on alone.

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.

Studying Protein Structures Illuminates Functions

Knowing the structures of proteins helps us understand the critical roles they play in health and disease and also points the way to designing new medicines. Protein structure determination is getting faster and cheaper thanks to a major NIGMS program called the Protein Structure Initiative (PSI). During the first 5 years of the PSI, nine pilot centers developed new tools and methods that enabled them to find the three-dimensional shapes of more than 1,300 proteins.

Ten new PSI research centers funded in FY 2005 plan to produce three times as many structures in the next 5 years. Four of the centers will use methods developed during the pilot period to rapidly determine the structures of proteins found in organisms ranging from bacteria to humans. Based on this information, scientists will be able to use computers to quickly and easily model the structures of a much larger number of proteins. An additional six smaller, more specialized centers will develop new methods for efficiently determining the structures of certain types of proteins that are particularly challenging to study.

As in the pilot phase, the newly funded PSI centers will submit their structures and related findings to the Protein Data Bank (http://www.rcsb.org/pdb/), a public repository of three-dimensional biological structure data that is supported by the National Science Foundation and NIH. From this repository, researchers can access an abundance of PSI-generated information that may help them better understand the function of proteins, predict the shapes of unknown proteins, identify new targets for drug development, and compare protein structures from normal and diseased tissues.

In FY 2006, the PSI will establish other resources for the scientific community. These include a centralized PSI Knowledgebase that will promote information integration, standardization, and dissemination and a PSI Materials Repository that will store and distribute resources generated by the PSI centers.

A key tool for protein structure determination is X-ray crystallography, which relies on X-ray beamlines at large, national facilities called synchrotrons. NIGMS, the National Cancer Institute, and the U.S. Department of Energy have collaborated since 2001 to build three innovative new X-ray beamlines at Argonne National Laboratory's Advanced Photon Source. The research community will have access to one of the beamlines in FY 2006, and all three will be fully operational in FY 2007.

PSI scientists have also made advances in nuclear magnetic resonance (NMR) spectroscopy, the other major tool for capturing data on protein structures. In FY 2005, Thomas A. Szyperski, Ph.D., of the University of Buffalo in New York developed a method that allowed his team to use NMR to solve eight protein structures in less than 20 days. This is in stark contrast to the time needed to solve just one structure using traditional NMR techniques, which can take up to a year.

Modeling the Spread of Infectious Diseases

The MIDAS program develops computer modeling techniques to analyze, predict, and respond to infectious disease outbreaks, whether they occur naturally or deliberately. This interdisciplinary network of scientists is modeling avian flu in an effort to understand how an outbreak in humans could spread and to identify effective strategies for containing the outbreak at its source.

As described in the science advances section, the researchers simulated outbreaks in Southeast Asia and have more recently turned their attention to developing models for the United States. Policymakers throughout the world are using information from MIDAS models in formulating plans to prepare for potential pandemic flu outbreaks.

Revealing Genetic Influence on Response to Medicines

The second phase of the NIH Pharmacogenetics Research Network began in FY 2005. This program, which NIGMS leads and eight other NIH components also fund, focuses on how a person's genes affect his or her response to medicines. This will maximize the benefits of treatment while minimizing adverse side effects, ultimately improving patient outcomes and reducing health care costs. During the first 5 years of the program, the research groups made critical advances in understanding the interactions between certain genes and drugs used to treat cancer, heart disease, asthma, and other diseases. The story of discovery highlights several of the most significant accomplishments of network scientists.

Laying the Foundation for Stem Cell Research

Although human embryonic stem cells hold great promise as a model system for research and for treating diseases, they pose several challenges: They are difficult to grow in the lab and scientists do not yet know how to reliably maintain them in their multipotential state or direct them to become a specific cell type.

To better understand the basic biology of human embryonic stem cells and establish the infrastructure needed to work with them, NIGMS funded three new Exploratory Centers for Human Embryonic Stem Cell Research in FY 2005. Each center will establish a core facility to support and train scientists, define optimal growth conditions and molecular characteristics for maintaining human embryonic stem cells, and support pilot projects to address some of the most fundamental questions regarding stem cell biology. The centers join three others that the Institute funded in FY 2003.

When the exploratory center grants expire, NIGMS is making plans to replace them with program project grants beginning in FY 2007. Each of these larger grants would include a core facility and at least three research projects addressing a basic question in human embryonic stem cell biology or chemistry relevant to the NIGMS mission. In addition to advancing scientists' ability to work with human embryonic stem cells, the grants would facilitate the use of the cells as an experimental model system.

Responding to the need for more skilled stem cell researchers who can advance the field, NIGMS led a group of NIH institutes in developing a new, ongoing program of fellowships in human embryonic stem cell research. The program was announced in FY 2005, and the first grants will be awarded in FY 2006.

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

Other Areas of Interest

Training the Next Generation of Scientists

NIGMS continues its long history of leadership in the area of research training, supporting nearly half of the predoctoral trainees and more than a quarter of all of the trainees who receive assistance from NIH. In recognition of the rapidly changing, interdisciplinary nature of biomedical and behavioral research today, the Institute's training programs cut across disciplinary and departmental lines and prepare 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 and behavioral 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. These plans are carefully evaluated, with the evaluations used in making funding decisions as well as in spurring continual improvement in the programs.

NIGMS trainees frequently contribute to significant research advances. In FY 2005, for example, a research team that included NIGMS predoctoral trainees discovered that toxic proteins involved in some neurodegenerative diseases, such as Huntington's, severely interfere with the cellular machinery responsible for removing damaged proteins within a cell. This finding could lead to new ways of treating and preventing these diseases.

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.

The MSTP supported 919 trainees in FY 2005. These exceptional students participated in a variety of research projects and helped make noteworthy findings, such as one that challenges an established view of how nerve cells communicate with each other. A better understanding of this fundamental process would have applications in the treatment of disorders that have been linked to abnormalities in neurotransmitter function, including depression, epilepsy, and autism. A

different MSTP trainee was the first author on a major journal article about the transmissibility of the 1918 pandemic influenza virus.

The Pharmacology Research Associate (PRAT) Program is a specialized training effort that constitutes the Institute's 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 molecular pharmacology, neurobiology, and cell signaling. In FY 2005, a PRAT fellow was part of a team that showed that a lab-made version of a human protein alleviates symptoms of both acute and chronic arthritis in mice and could be the basis for a new arthritis drug for people.

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. In FY 2005, NIGMS and other NIH institutes awarded grants to support the first 23 trainees in this program. Future grants will be supported solely by NIGMS.

Another new activity addresses the serious shortage of scientists trained in the study of how organ systems and whole organisms respond to drugs and other physiological stimuli. In FY 2005, NIGMS funded four short courses that offered intensive, hands-on experiences in this area, which has applications in the fields of pharmacology, physiology, and toxicology.

Enhancing Behavioral Research and Training

NIGMS funds basic behavioral research in areas that include the genetic and biochemical mechanisms underlying behavior, 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 supports the development of genetic tools and genomic resources that enable researchers to exploit the full potential of such model systems. Building on the opportunities in this area, in October 2005 NIGMS and the National Institute of Child Health and Human Development jointly announced their interest in supporting collaborations involving behavioral scientists and investigators who have expertise in molecular biology or genomics. One objective of these collaborations is the development of new animal models and the enhancement of existing models for behavioral research.

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 Neuroscience Blueprint, which has a significant behavioral component.

NIGMS funds some research training in the behavioral sciences through institutional grants, 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). MORE also funds graduate fellowships in the behavioral sciences, and the NIGMS Division of Genetics and Developmental Biology funds postdoctoral fellowships in neurogenetics and the genetics of behavior.

To capitalize on the wealth of opportunities that exist at the intersection of the biological and behavioral sciences, NIGMS is working with other NIH components to develop an innovative new training program in this interface area. The Institute expects to fund the first grants in this program in FY 2007.

Targeting AIDS Through Research and Training

NIGMS support related to AIDS currently 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. Scientists supported by this program continue to advance our understanding of the virus using the tools of structural biology. In FY 2005, for example, a grantee determined the structure of a rare human antibody that essentially neutralizes HIV particles, possibly offering a new direction for designing an effective AIDS vaccine.

Although researchers have determined the structures of many HIV proteins in isolation, they know the structures of only a few HIV proteins interacting with cellular components. Because HIV works through such interactions, knowing the structures of more of these complexes will provide targets for new generations of anti-AIDS drugs.

To speed progress toward this goal, in FY 2007 NIGMS plans to replace the expiring program project grants with two to three new centers for the determination of the structures of additional complexes between HIV proteins and cellular components. The centers will take advantage of the technologies developed through the Protein Structure Initiative and will be complemented by individual, investigator-initiated research grants that are linked to the centers and funded by the National Institute of Allergy and Infectious Diseases.

Joining Forces for Neuroscience

The NIH Neuroscience Blueprint enhances cooperative activities among NIGMS and 14 other NIH institutes and centers that support research on the nervous system. By pooling resources and expertise, the Blueprint benefits from economies of scale, confronts challenges too large for any single institute or center, and develops research tools and infrastructure that serve the entire neuroscience community. This approach allows the broad implementation of best practices developed at a single institute or center, the coordination of planning at the early concept stage, the expansion of access to neuroscience resources, and the creation of multi-institute working groups to focus on cross-cutting scientific issues.

One element of the Blueprint that NIGMS is funding is the NIH Neuroscience Microarray Consortium. This resource provides NIH-supported scientists with access to state-of-the-art technologies for profiling gene activity and identifying genetic sequence variations. To speed

research progress, the consortium deposits data in a shared database, and it also offers technical assistance, reagents, and other services at a reasonable cost.

Increasing Minority Opportunities in Research

NIGMS has a strong commitment to increasing the number of minority biomedical and behavioral scientists. The focal point for this effort is the Division of Minority Opportunities in Research, which encourages minority students to pursue training for scientific careers and enhances science curricula and faculty research capabilities at institutions with substantial minority enrollments. MORE's main components are Minority Access to Research Careers (MARC), Minority Biomedical Research Support (MBRS), and special initiatives.

Minority Access to Research Careers

MARC supports student and faculty research training and helps institutions with substantial minority enrollments strengthen their biomedical research training capabilities. As a result, these schools are better able to interest and prepare students for doctoral studies and biomedical research careers. In FY 2005, MARC supported 664 undergraduate students at 56 institutions, 157 predoctoral fellows, and 2 faculty fellows.

Minority Biomedical Research Support

MBRS awards grants to institutions with substantial minority enrollments to support research by faculty members, strengthen the institutions' biomedical research capabilities, and provide opportunities for students to work as part of a research team. In FY 2005, 840 faculty members at 111 institutions worked on 421 research projects. MBRS also supported 1,392 undergraduate and 582 graduate students who worked as research assistants on scientific projects at their own institutions or in other settings, including laboratories at research-intensive institutions.

Special Initiatives

Several MORE initiatives take new approaches to recruiting and retaining minority biomedical scientists. One of them, Bridges to the Future, assists students in associate's or master's degree programs in making the sometimes-difficult transition to the next level of training (the bachelor's or Ph.D. degree). Since the program's inception in 1992, NIGMS and the program's co-sponsor, the NIH National Center on Minority Health and Health Disparities, have funded 165 grants, 6 of which received initial support in FY 2005.

Two innovative programs foster career development at the postdoctoral and faculty levels. The Institutional Research and Academic Career Development Award provides postdoctoral researchers with teaching experience at minority-serving institutions. The ancillary benefits of this program include motivating the next generation of minority scientists and promoting linkages between research-intensive universities and minority-serving institutions. The Faculty Development Award enables minority institution faculty members to enhance their research skills by working in a laboratory at a research-intensive university.

A partnership with the Indian Health Service links the Native American community with organizations that conduct health research. This program encourages research on diseases relevant to American Indians and Alaska Natives while also preparing Native American scientists and health professionals to compete for NIH funding.

In addition to the activities described above, MORE supports workshops and mini-courses on a number of topics, including grant writing and program evaluation. It also funds studies of the effectiveness of interventions to increase minority and other student interest, motivation, and preparedness for biomedical and behavioral research careers. Finally, MORE plays a key role in supporting two of the largest scientific meetings of minority scientists, the Annual Biomedical Research Conference for Minority Students and the annual meeting of the Society for Advancement of Chicanos and Native Americans in Science.

Successful Results

Many MORE participants move on to productive scientific careers in academia, industry, or government. This shows the benefit of an educational strategy that involves students in hands-on research experiences.

A prime example is Erich Jarvis, Ph.D., an associate professor at Duke University Medical Center in Durham, NC, who participated in the MARC and MBRS programs as an undergraduate and graduate student. Jarvis was one of only 13 scientists in the country to receive a 2005 NIH Director's Pioneer Award. He plans to use the award to study the genetic machinery underlying vocal learning.

Other MORE success stories include:

- Michael Anderson, Ph.D., who received MARC undergraduate support and is now a postdoctoral fellow at Johns Hopkins University in Baltimore, MD;
- Tracy Ferea, Ph.D., who received MARC undergraduate and MBRS predoctoral support before becoming a research scientist at Applied Biosystems in Palo Alto, CA; and
- Belinda Pastrana-Rios, Ph.D., an MBRS participant at the undergraduate and graduate levels who is now an associate professor of chemistry at the University of Puerto Rico, Mayaguez.

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. For example, in FY 2005 the Institute took several important steps toward the goal of a highly secure, integrated electronic work environment.

In one prong of this effort, NIGMS staff began using an electronic document management system that enables them to store and organize documents, share material within and across

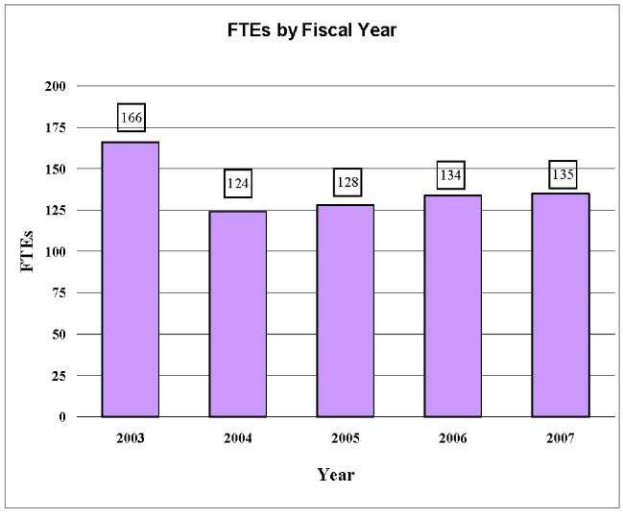
organizational units, and implement electronic workflow procedures. By moving to an almost entirely electronic workflow for its grants processes, the Institute will virtually eliminate costs associated with creating and maintaining paper files and with distributing paper copies of grant-related documents. On another front, the Institute moved its Intranet and Internet sites to an NIH-operated content management system and integrated the Intranet site with the NIH portal. This allows any NIH employee to access the wealth of valuable information on the site. Sharing Intranet content in this way is expected to reduce the time and effort required to develop certain types of policies and procedures across NIH, since staff members can now find and customize an existing document rather than having to create completely new material.

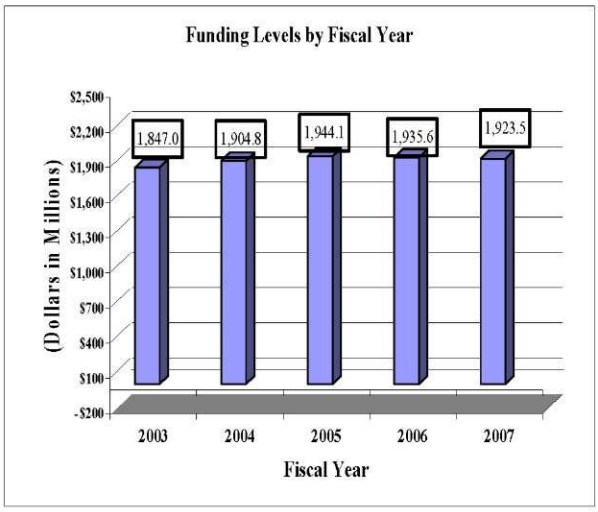
In the financial management arena, NIGMS expanded the use of its highly successful—and emulated—electronic checkbook system. The system is now helping NIGMS staff track budgets for the substantial number of activities the Institute is leading within the NIH Roadmap and other trans-NIH initiatives.

Budget Policy

The Fiscal Year 2007 budget request for the NIGMS is $1,923,481,000, a decrease of $12,137,000 and 0.6 percent from the FY 2006 Appropriation. Included in the FY 2007 request is NIGMS's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. 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 as the result of several administrative restructurings in recent years, FTE data is non-comparable.





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 $325,000 in FY 2007. While no inflationary increases are provided for

direct recurring costs in noncompeting RPGs, where the NIGMS has committed to a programmatic increase for an award, such increases will be provided.

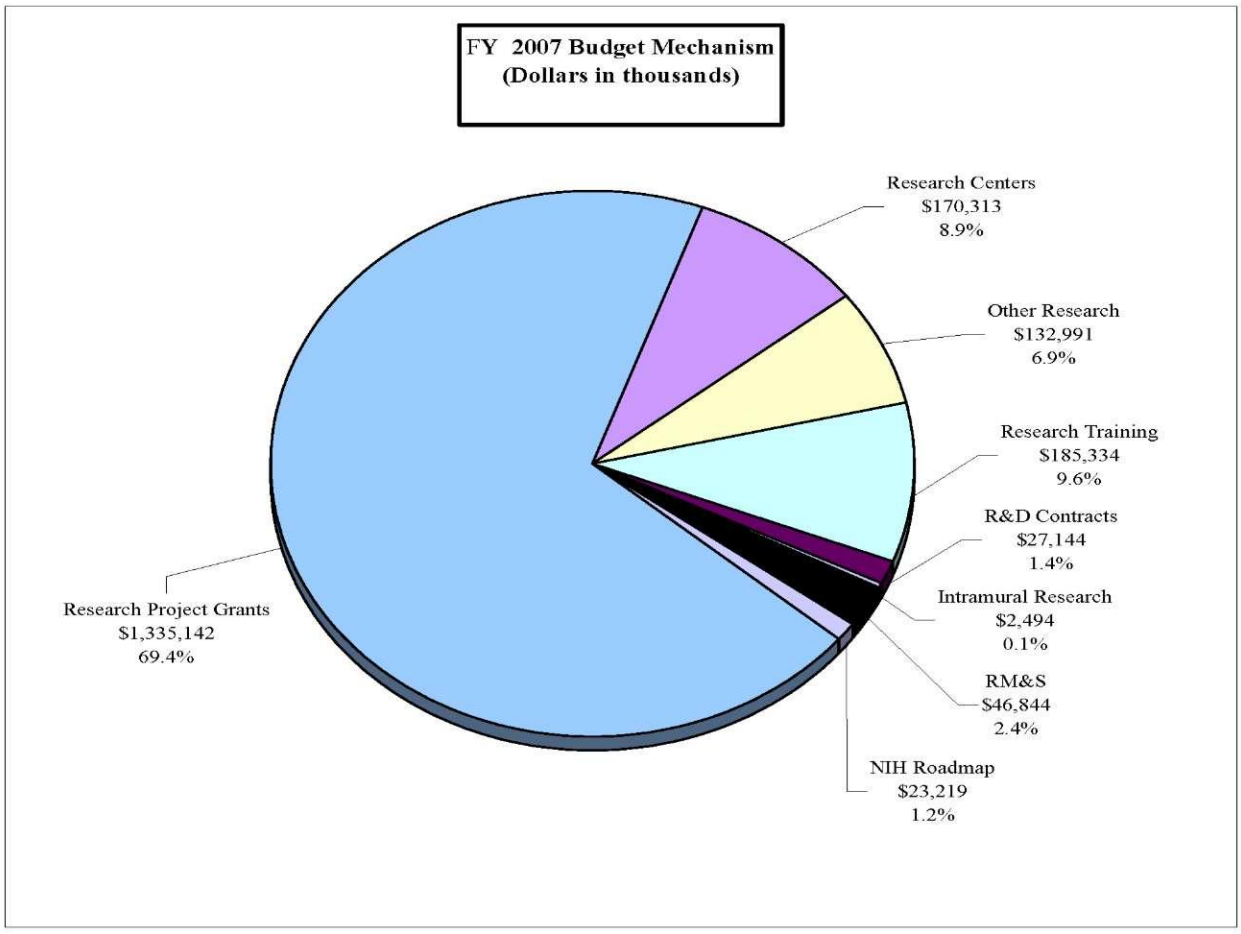
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIGMS, $1.1 million will be used to support 12 awards for the new K/R "Bridges to Independence" program.

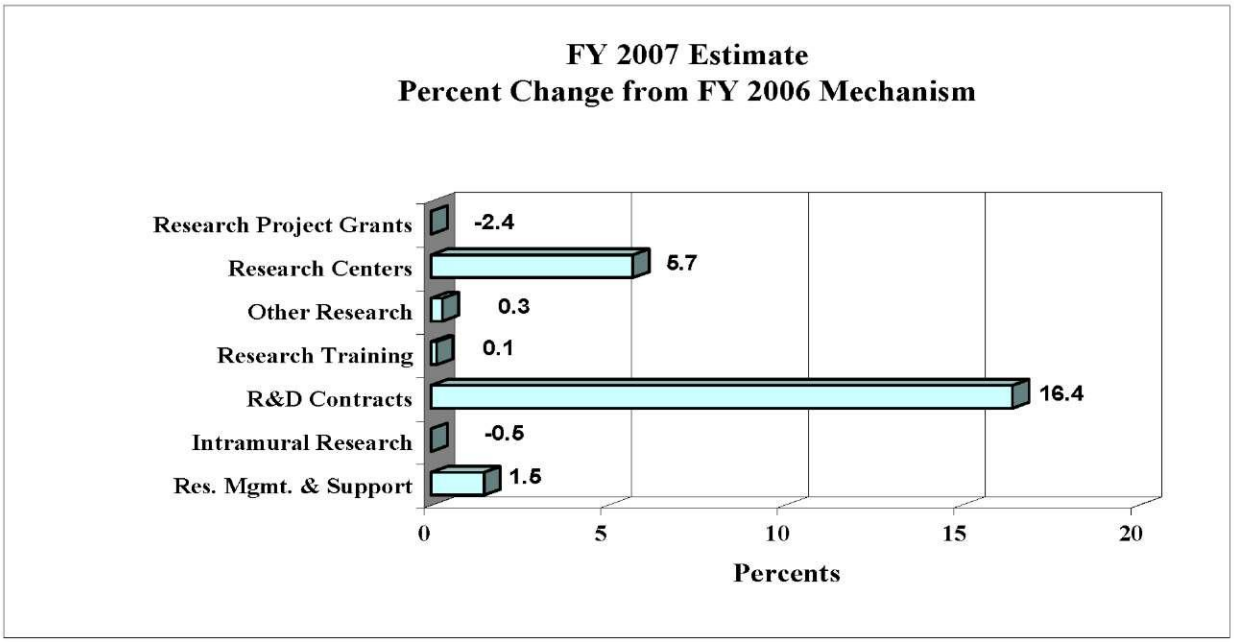
NIGMS will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $3,228,000 to support this project.

In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 56 research centers, 331 other research grants, including 64 career awards, and 29 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent.

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





NATIONAL INSTITUTES OF HEALTH
National Institute General Medical Sciences

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,002	$1,005,076,000	2,913	$1,008,472,000	2,767	$962,605,000
Administrative supplements	(245)	15,360,000	(245)	15,206,000	(245)	15,130,000
Competing:						
Renewal	508	185,541,000	600	212,409,000	636	224,685,000
New	450	126,838,000	316	86,332,000	323	88,061,000
Supplements	5	867,000	5	840,000	5	838,000
Subtotal, competing	963	313,246,000	921	299,581,000	964	313,584,000
Subtotal, RPGs	3,965	1,333,682,000	3,834	1,323,259,000	3,731	1,291,319,000
SBIR/STTR	160	45,454,000	156	44,341,000	154	43,823,000
Subtotal, RPGs	4,125	1,379,136,000	3,990	1,367,600,000	3,885	1,335,142,000
Research Centers:						
Specialized/comprehensive	54	160,422,000	54	158,638,000	56	167,844,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	2,058,000	0	2,057,000	0	2,047,000
Comparative medicine	0	431,000	0	424,000	0	422,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	54	162,911,000	54	161,119,000	56	170,313,000
Other Research:						
Research careers	52	12,951,000	52	12,809,000	64	13,825,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	143	102,104,000	142	100,981,000	141	100,476,000
Other	128	17,519,000	127	18,784,000	126	18,690,000
Subtotal, Other Research	323	132,574,000	321	132,574,000	331	132,991,000
Total Research Grants	4,502	1,674,621,000	4,365	1,661,293,000	4,272	1,638,446,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	607	25,014,000	597	25,607,000	597	25,479,000
Institutional awards	3,884	160,802,000	3,815	159,452,000	3,845	159,855,000
Total, Training	4,491	185,816,000	4,412	185,059,000	4,442	185,334,000
Research & development contracts	28	23,569,000	28	23,310,000	29	27,144,000
(SBIR/STTR)	(0)	(102,000)	(0)	(101,000)	(0)	(100,000)
	FTEs		FTEs		FTEs	
Intramural research	13	2,522,000	13	2,507,000	12	2,494,000
Research management and support	115	45,249,000	121	46,152,000	123	46,844,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	0	12,290,000	0	17,297,000	0	23,219,000
Total, NIGMS	128	1,944,067,000	134	1,935,618,000	135	1,923,481,000
(Clinical Trials)		(0)		(0)		(0)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

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Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2005 Actual FTEs	FY 2005 Actual Amount	FY 2006 Appropriation FTEs	FY 2006 Appropriation Amount	FY 2007 Estimate FTEs	FY 2007 Estimate Amount	Change FTEs	Change Amount
Extramural Research: Biomedical Research and Research Training		$1,884,006		$1,869,662		$1,850,924		($18,738)
Subtotal, Extramural research		1,884,006		1,869,662		1,850,924		(18,738)
Intramural research	13	2,522	13	2,507	12	2,494	(1)	(13)
Res. management & support	110	45,249	115	46,152	117	46,844	2	692
NIH Roadmap for Medical Research	5	12,290	6	17,297	6	23,219	0	5,922
Total	128	1,944,067	134	1,935,618	135	1,923,481	1	(12,137)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
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Summary of Changes

FY 2006 Estimate				$1,935,618,000
FY 2007 Estimated Budget Authority				1,923,481,000
Net change				(12,137,000)
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$1,196,000		$21,000
b. Annualization of January 2006 pay increase		1,196,000		9,000
c. January 2007 pay increase		1,196,000		20,000
d. Payment for centrally furnished services		154,000		2,000
e. Increased cost of laboratory supplies, materials, and other expenses		1,157,000		27,000
Subtotal				79,000
2. Research Management and Support:				
a. Within grade increase		14,935,000		260,000
b. Annualization of January 2006 pay increase		14,935,000		116,000
c. January 2007 pay increase		14,935,000		246,000
d. Payment for centrally furnished services		12,062,000		181,000
e. Increased cost of laboratory supplies, materials, and other expenses		19,155,000		494,000
Subtotal				1,297,000
Subtotal, Built-in				1,376,000

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Summary of Changes--continued

CHANGES	2006 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,913	$1,023,678,000	(146)	($45,943,000)
b. Competing	921	299,581,000	43	14,003,000
c. SBIR/STTR	156	44,341,000	(2)	(518,000)
Total	3,990	1,367,600,000	(105)	(32,458,000)
2. Research centers	54	161,119,000	2	9,194,000
3. Other research	321	132,574,000	10	417,000
4. Research training	4,412	185,059,000	30	275,000
5. Research and development contracts	28	23,310,000	29	3,834,000
Subtotal, extramural				(18,738,000)
	FTEs		FTEs	
6. Intramural research	13	2,507,000	(1)	(92,000)
7. Research management and support	115	46,152,000	2	(605,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Buildings and Facilities		0		0
11. NIH Roadmap for Medical Research	6	17,297,000	0	5,922,000
Subtotal, program		1,935,618,000		(13,513,000)
Total changes	134		1	(12,137,000)

NATIONAL INSTITUTES OF HEALTH
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Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	134	135	1
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$159,508	$163,405	$3,897
Average GM/GS grade	12.2	12.2	0.0
Average GM/GS salary	$101,816	$104,303	$2,487
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$0	$0	$0
Average salary of ungraded positions	120,990	123,946	2,956

	OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$6,607,000	$6,924,000	$317,000
11.3	Other than Full-Time Permanent	6,060,000	6,351,000	291,000
11.5	Other Personnel Compensation	400,000	419,000	19,000
11.7	Military Personnel	0	0	0
11.8	Special Personnel Services Payments	0	0	0
	Total, Personnel Compensation	13,067,000	13,694,000	627,000
12.0	Personnel Benefits	3,064,000	3,210,000	146,000
12.2	Military Personnel Benefits	0	0	0
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Costs	**16,131,000**	**16,904,000**	**773,000**
21.0	Travel & Transportation of Persons	370,000	370,000	0
22.0	Transportation of Things	14,000	14,000	0
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	5,000	5,000	0
23.3	Communications, Utilities & Miscellaneous Charges	178,000	178,000	0
24.0	Printing & Reproduction	857,000	856,000	(1,000)
25.1	Consulting Services	337,000	335,000	(2,000)
25.2	Other Services	4,772,000	4,765,000	(7,000)
25.3	Purchase of Goods & Services from Government Accounts	85,502,000	89,270,000	3,768,000
25.4	Operation & Maintenance of Facilities	61,000	61,000	0
25.5	Research & Development Contracts	2,992,000	2,977,000	(15,000)
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	1,134,000	1,132,000	(2,000)
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**94,798,000**	**98,540,000**	**3,742,000**
26.0	Supplies & Materials	234,000	233,000	(1,000)
31.0	Equipment	293,000	293,000	0
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,805,441,000	1,782,869,000	(22,572,000)
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	**1,902,190,000**	**1,883,358,000**	**(18,832,000)**
	NIH Roadmap for Medical Research	**17,297,000**	**23,219,000**	**5,922,000**
	Total Budget Authority by Object	**1,935,618,000**	**1,923,481,000**	**(12,137,000)**

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute General Medical Sciences

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$6,607,000	$6,924,000	$317,000
Other Than Full-Time Permanent (11.3)	6,060,000	6,351,000	291,000
Other Personnel Compensation (11.5)	400,000	419,000	19,000
Military Personnel (11.7)	0	0	0
Special Personnel Services Payments (11.8)	0	0	0
Total Personnel Compensation (11.9)	**13,067,000**	**13,694,000**	**627,000**
Civilian Personnel Benefits (12.1)	3,064,000	3,210,000	146,000
Military Personnel Benefits (12.2)	0	0	
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**16,131,000**	**16,904,000**	**773,000**
Travel (21.0)	370,000	370,000	0
Transportation of Things (22.0)	14,000	14,000	0
Rental Payments to Others (23.2)	5,000	5,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	178,000	178,000	0
Printing and Reproduction (24.0)	857,000	856,000	(1,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	29,000	29,000	0
Other Services (25.2)	4,772,000	4,765,000	(7,000)
Purchases from Govt. Accounts (25.3)	26,594,000	28,283,000	1,689,000
Operation & Maintenance of Facilities (25.4)	0	0	0
Operation & Maintenance of Equipment (25.7)	1,134,000	1,132,000	(2,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**32,529,000**	**34,209,000**	**1,680,000**
Supplies and Materials (26.0)	234,000	233,000	(1,000)
Subtotal, Non-Pay Costs	34,187,000	35,865,000	1,678,000
Total, Administrative Costs	**50,318,000**	**52,769,000**	**2,451,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

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

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Anesthesiology research - The Committee urges NIGMS to continue to support and enhance research opportunities focused on discovering the mechanisms of anesthesia, perfecting agents for regional and general anesthesia, improving the safety of anesthesia, monitoring and protection of specific organs of patients under anesthesia and optimizing post-surgery prognosis. The Committee encourages NIGMS to continue to work with other appropriate Institutes to promote improvements in pain research. The Committee believes that NIGMS should strongly support training, innovation and scientific inquiry in these crucial areas of medical research. (p. 80)

Action taken or to be taken

NIGMS continues to support a portfolio of research grants dedicated to understanding the underlying mechanisms of anesthetics, both general and local, and their effects on integrated organ systems. The overall goal of this research is to improve the effectiveness and safety of these important drugs, and to help develop novel anesthetics. This long-standing research program includes individual investigator-initiated grants, multi-component program project grants, and small business awards. In FY2005, NIGMS awarded $26,683,053 in total direct costs to grants in this research program. In addition, NIGMS is committed to the training and career development of young clinician scientists in the field of anesthesiology and offers career development (K) awards and institutional training grants specifically for this purpose. NIGMS cooperates with other NIH institutes, centers and offices on the NIH Pain Consortium, whose goal includes developing a comprehensive pain research agenda for NIH, and identifying key opportunities in pain research.

Item

Cystic fibrosis (CF) - The Committee commends NIGMS for the renewal and expansion of its large-scale collaborative project awards. These cross-disciplinary, multi-institutional collaborative projects are important for moving burgeoning fields faster than through traditional investigator-initiated grants. The Committee encourages NIGMS to consider support for research on the barriers to productive protein folding and the creation of tools, reagents and advances in techniques for precision monitoring of folding. These tools will support ongoing research efforts to understand the underlying mechanisms of disease caused by improper protein folding, as well as efforts to develop therapies to correct this defect for CF and other diseases. (p. 80)

Action taken or to be taken

When scientists, like Jacinto Steinhardt, Charles Tanford and Nobel laureate Christian Anfinsen, studied protein folding fifty years ago, the goal was simply to understand how proteins went from a more or less random, extended rope-like structure to a discreet compact folded conformation. In recent years, researchers supported by NIGMS have determined that protein folding is a process fundamental to life. Understanding protein folding has taken on new urgency because of the involvement of misfolded proteins in a number of common diseases, including Alzheimer's disease and cystic fibrosis.

The most common form of cystic fibrosis is caused by the deletion of a single amino acid in a protein that is responsible for the transport of chloride through membranes. Absence of this transporter causes problems in mucous secretion in many parts of the body, with especially damaging effects in the lungs and pancreas. Research has shown that the defective transport protein produced in individuals with cystic fibrosis is not completely folded into its proper shape, although it is still partially capable of doing its job, if it reaches the right part of the cell. Unfortunately, the body's own quality control system, meant to assure that only perfect proteins survive, considers the improperly folded cystic fibrosis protein to be defective and destroys it before it can be put to use. For the past several years, several NIGMS grantees have been studying this process at the level of basic biology. For example, NIGMS grantee Douglas Cyr has recently shown that it may be possible to block the degradation pathway of the defective channel protein, allowing the partially functional cystic fibrosis protein to survive and do its job.

Understanding how the cystic fibrosis protein normally folds, and how the protein interacts with the quality control machinery when it fails to fold, provides new routes to possible treatments. Especially for a genetic defect like cystic fibrosis, research is focused on finding drugs that can either increase the proper folding of the protein or increase or decrease the action of the quality control machinery as needed.

Item

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 encourages 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. 80)

Action taken or to be taken

NIGMS, through its Division of Minority Opportunities in Research (MORE), continues to support a portfolio of research training grants dedicated to the development of underrepresented minority scientists. The overall goal of MORE is to significantly increase the number of

individuals from minority groups underrepresented in biomedical sciences that participate fully in the biomedical research enterprise of this country. MORE does this through programs of its Minority Access to Research Careers (MARC) and its Minority Biomedical Research Support (MBRS) Branches. In order to increase the enrollment of competitively trained underrepresented minority students in Ph.D. or MD/Ph.D. programs to prepare for research careers in the biomedical sciences, the MARC Branch focuses on undergraduate research training, supporting both institutional research training grants and grants for ancillary training activities. In FY 2005, the MARC institutional research training grants supported approximately 648 undergraduate students, many of whom attended historically black colleges and universities (HBCUs) or historically black health professions schools. The MBRS Branch supports undergraduates through its Research Initiative for Scientific Enhancement (RISE). The purpose of the RISE program is to enhance the research training environment at minority serving institutions, such as HBCUs, and to increase the numbers of students who pursue and attain the Ph.D. degree. In FY 2005, the RISE program supported the research development of approximately 1079 underrepresented minority students, most of whom were undergraduates. NIGMS and MORE remain committed to supporting programs to engage underrepresented undergraduates in preparing for careers in biomedical research.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Basic Behavioral Research – The Committee notes the lack of a positive response to Congressional requests that the NIH establish a basic behavioral research and training program within the National Institute of General Medical Sciences as authorized within the statutory language establishing the Institute. The Committee notes that this recommendation was also made to the Director of NIH by a special task force created by the NIH to review this matter. The Committee believes that this research will support important advances in understanding the wide range of fundamental behavioral topics relevant to a variety of diseases and health conditions. The Committee strongly urges the NIGMS to consider establishing a basic behavioral research and training program as part of its portfolio, especially in the areas of learning, memory, and cognition; behavioral neuroscience; behavioral genetics; the biological basis of behavior; behavior change; stress; psychophysiology; social psychology; methodology and evaluation; and experimental psychology. (p. 121)

Action Taken and to be Taken

In October, 2005, the National Institute of General Medical Sciences (NIGMS) issued a program announcement, *Collaborative Research for Molecular and Genomic Studies of Basic Behavior in Animal Models* (PA-06-038), to stimulate basic behavioral research in model systems. Research funded through this announcement will support collaborations between behavioral scientists and investigators with expertise in state-of-the-art genetics, molecular biology, and genomics. NIGMS has also taken the lead in developing plans for a trans-NIH research training program to promote interdisciplinary research at the interface of the behavioral and biological sciences. At least 12 institutes have expressed interest in joining NIGMS in this effort.

In the House Appropriations Committee Conference Report 109-300 (p. 78), the NIH is urged to "...develop a structural framework for managing support of NIH basic behavioral science research... The conferees request a report to the House and Senate Appropriations Committees describing the new framework and its relationship to the Office of Portfolio Analysis and Strategic Initiatives by May 1, 2006." This report will address similar issues raised in Senate Report 109-103. The National Institute of General Medical Sciences, along with other NIH institutes and centers, will work cooperatively with the NIH Office of Behavioral and Social Sciences Research to prepare this report by the May deadline.

Item

Basic Behavioral Research in Roadmap – The Committee requests that NIGMS study the feasibility of developing one or more funding initiatives specific to basic behavioral and social sciences research, which is significantly underrepresented in the New Pathways to Discovery segment. (p. 121)

Action Taken

Although it is not considered part of the New Pathways to Discovery portion of the NIH Roadmap, the National Institute of General Medical Sciences took a leading role in developing *Collaborations with National Centers for Biomedical Computing* (PAR-05-063), a solicitation for projects to collaborate with the recently-formed NIH Roadmap for Medical Research National Centers for Biomedical Computing (NCBCs). The major goal of this program announcement is to provide the resources for a wide range of biomedical, behavioral, and computational researchers to establish new collaborations with the NIH NCBCs. Areas of research cited in the announcement include, but are not limited to, behavioral science, decision-making, cognitive science, and substance abuse research.

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students in conjunction with historically black health professions schools. The Committee urges continued, long-term support of this program. (p. 121-122)

Action taken or to be taken

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NATIONAL INSTITUTES OF HEALTH
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Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,750,559,000	Indefinite	$1,738,147,000
Sciences	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	185,059,000		185,334,000
Total, Budget Authority				1,935,618,000		1,923,481,000

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

NATIONAL INSTITUTES OF HEALTH
National Institute General Medical Sciences

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1998	992,032,000 2/	1,047,963,000	1,058,969,000	1,065,947,000
1999	1,111,439,000 2/ 3/	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	1,706,968,000	1,753,465,000	1,725,263,000
Rescission				(124,000)
2003	1,874,243,000	1,874,243,000 4/	1,853,584,000	1,859,084,000
Rescission				(12,084,000)
2004	1,923,133,000	1,923,133,000 4/	1,917,033,000	1,916,333,000
Rescission				(11,495,000)
2005	1,959,810,000	1,959,810,000 4/	1,975,500,000	1,959,810,000
Rescission				(15,743,000)
2006	1,955,170,000	1,955,170,000 4/	2,002,622,000	1,955,170,000
Rescission				(19,552,000)
2007	1,923,481,000			

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

NATIONAL INSTITUTES OF HEALTH
National Institute General Medical Sciences

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	15	15	15
Office of Scientific Review	8	9	9
Office of Administrative Management	22	22	22
Division of Extramural Activities	33	34	34
Division of Genetic and Developmental Biology	8	9	9
Division of Pharmacology, Physiology, and Biological Chemistry	21	21	21
Division of Cell Biology and Biophysics	11	12	12
Center of Bioinformatics and Computational Biology	0	1	2
Division of Minority Opportunities in Research	5	5	5
NIH Roadmap for Medical Research	5	6	6
Total	128	134	135
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2003	10.9
2004	12.3
2005	12.2
2006	12.2
2007	12.2

NATIONAL INSTITUTES OF HEALTH
National Institute General Medical Sciences

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	1	1	1
Total - ES Salary	$154,440	$159,508	$163,405
GM/GS-15	11	11	11
GM/GS-14	12	14	14
GM/GS-13	21	21	22
GS-12	12	12	12
GS-11	6	6	6
GS-10	0	0	0
GS-9	4	4	4
GS-8	3	3	3
GS-7	4	4	4
GS-6	0	0	0
GS-5	1	1	1
GS-4	0	0	0
GS-3	1	1	1
GS-2	0	0	0
GS-1	0	0	0
Subtotal	75	77	78
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade			
Senior Grade	0	0	0
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	0	0	0
Ungraded	50	54	54
Total permanent positions	75	77	78
Total positions, end of year	126	132	132
Total full-time equivalent (FTE) employment,end of year	128	134	135
Average ES salary	$154,440	$159,508	$163,405
Average GM/GS grade	12.2	12.2	12.2
Average GM/GS salary	$98,581	$101,816	$104,303

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
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New Positions Requested

	FY 2007		
	Grade	Number	Annual Salary
Health Science Administrator	GS-13	1	$95,697
Total Requested		1	