Justification

National Institute of General Medical Sciences

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

Budget Authority:

FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
171	$1,371,146,000	176	$1,540,194,000	180	$1,720,206,000	4	$180,012,000

This document provides justification for the Fiscal Year 2002 activities of the National Institute of General Medical Sciences (NIGMS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2002 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

NIGMS supports the foundation of biomedical research: the study of how biological molecules and systems work. Good health depends on the proper action of these molecules and systems, and disease can result when they malfunction.

In keeping with its role, NIGMS has programs that cover a broad range of scientific areas, including cell biology, biophysics, genetics, chemistry, and pharmacology. The Institute also has programs to train future scientists and to increase the number of minority biomedical researchers.

During FY 2000, NIGMS began funding three major research initiatives that it created to stimulate highly promising areas of biomedical science. The largest of these activities will determine the three-dimensional structures of thousands of proteins.

Why is knowing a protein's structure important? Because proteins are the workhorses of the body. They help digest food, allow blood to carry oxygen, fight infections, and perform many other critical jobs. A protein's function often depends on its structure. Determining the detailed structures of proteins will help scientists understand how proteins function normally and how faulty protein structures can cause disease. Scientists can also use the structures of disease-related proteins to develop new medicines or diagnostic techniques.

Determining protein structures is a difficult, time-consuming task. By comparison, deciphering gene sequences--the "recipes" for proteins--is quick and easy. So for decades, researchers have looked for a shortcut to protein structure determination by trying to predict structures from the

limited number of gene sequences that were known. The recent explosion of available gene sequences and advances in the methods for determining protein structures make the time right for the NIGMS Protein Structure Initiative.

Scientists involved in the Protein Structure Initiative are starting by organizing all known proteins into "families" based on their gene sequences. The researchers will then determine the structure of one or more representative proteins from each family, for a total of about 10,000 structures. These structures will teach the researchers valuable lessons about the relationship between gene sequence and protein structure. With this knowledge as a guide, the scientists hope to use gene sequences to predict the structures of many other proteins. Researchers call this effort "structural genomics."

The second NIGMS research initiative focuses on pharmacogenetics, which examines how a person's genes influence his or her responses to medicines. Pharmacogenetics has the potential to revolutionize medical treatment by making it possible to develop new medicines as well as to tailor the selection and dose of a medicine to a person's genetic make-up.

The third Institute research initiative provides support to "glue together" groups of investigators working on significant problems that could not be solved if the scientists worked independently. Like the other two initiatives, it involves the formation of a network of researchers who collaborate and share their results to speed progress toward a major goal. All of these initiatives reflect changes in how biomedical research is done today. There is an increased emphasis on large-scale and collaborative approaches to important scientific questions. These include studies of complex processes that involve the interaction of many components, such as all of the activities that go on within a single cell and the ways that cells and organs "talk" to each other.

Studying complex processes requires the contributions of more than just biological scientists, though. It requires the expertise and approaches of physicists, mathematicians, computer scientists, and engineers, all of whom are in a unique position to organize and analyze the vast amounts of data generated by studies of complex systems. NIGMS has started programs to encourage these scientists to join their expertise and interests with those of biomedical researchers.

The story of discovery and science advances that follow provide a taste of the new insights into biological processes and disease mechanisms that are flowing from NIGMS-funded studies. The material also shows some of the ways in which this research leads to therapeutic benefits in the form of new medicines, medicine dosages tailored to the responses of individual patients, and new approaches to treatment.

Story of Discovery:
A Century of Fruit Fly Research Sheds Light on Human Health and Disease

In March 2000, a team of scientists announced that it had unscrambled the genetic code of a tiny fruit fly called *Drosophila melanogaster*. Within a week, dozens of stories about this scientific *tour de force* appeared in newspapers and magazines around the world. Why did the media pay so much attention? The *Drosophila* genome was the largest genetic code unscrambled thus far, and the completion of this project in record time validated a method later used to sequence the human genome.

Another reason for the media interest is the similarities between human and fly genes. Of the 289 human genes that, when "misspelled," are known to cause diseases in people, 177 have direct counterparts in the fruit fly. A complete catalog of fly genes is an extraordinary tool that will help researchers understand how genes work--not only in flies, but also in humans and other organisms. The achievement is a boon to the thousands of scientists who study human health using the fruit fly, which is one of a number of valuable model systems that aid researchers in making breakthroughs in the fight against disease.

Drosophila became a model system for studying how genes work nearly 100 years ago, when Dr. Thomas Hunt Morgan, then at Columbia University, found an unusual fruit fly on his laboratory wall. This fly's eyes were white instead of the usual red. Years later, researchers discovered that this strain of fruit fly had white eyes because one of the fly's genes hadn't worked properly. These observations touched off an enormously productive field of study. For decades, NIGMS- and other NIH-supported basic scientists have used the fruit fly model system to make connections between specific genes, normal and abnormal development, and disease in animals, including humans. Some of their achievements are described below.

In the 1970s, Dr. Edward Lewis and his coworkers at the California Institute of Technology pinpointed the genes that control the development of body segments, features that make a fruit fly recognizable as an insect. This finding set the stage for other scientists to discover that the same genes control developmental patterning processes in humans, who do not have recognizable segments. Around that time, researchers studying development in fruit flies began to devote their attention to organs, particularly the eyes, the ovaries, and the testes. Dr. Seymour Benzer, also at the California Institute of Technology, found fly eyes to be convenient targets. He and his colleagues could easily identify important eye genes because the loss of these genes impairs flies' ability to run toward light. Ovaries and testes intrigued scientists for a different reason. Dr. Thomas Cline of the University of California, Berkeley and Dr. Bruce Baker of Stanford University reasoned that since only females have ovaries and only males have testes, they could study the genes that affect these organs to figure out why the organs develop differently in the two sexes and apply that knowledge to understanding human development.

Dr. Charles Zuker of the University of California, San Diego identified certain genes that, when they malfunction, make a fly's eyes degenerate, causing blindness. Scientists now know that the genes that cause eye degeneration in flies are also present in humans. Mutations in these human genes are responsible for many cases of macular degeneration, the most common cause of blindness in adults. Detailed studies of the fly genes that cause eye degeneration should provide clues about how to correct--or even prevent--macular degeneration in people. Throughout the 1980s and 1990s, fly researchers studied the development of other organs, particularly the heart, the brain, and the respiratory system. Dr. Mark Krasnow and his coworkers at Stanford University School of Medicine discovered that a growth-promoting molecule called "branchless" directs the proper development of fly respiratory tubules--a network of large and small pipe-like structures that carry oxygen into a fly's body. Recently, the scientists found that this protein's ability to regulate the development of small respiratory tubules is controlled by oxygen. Something very similar happens in human embryos, where oxygen-regulated growth factors initially control the development of the major blood vessels and later control the development of the smaller capillaries. The striking parallel between the development of the fly respiratory system and the human circulatory system promises to help researchers better understand how blood vessel overgrowth sustains cancer cells, and possibly how enhancing the growth of oxygen-carrying vessels may help treat heart disease.

Fruit flies have been important tools for studies of the brain and diseases that impair the function of the central nervous system. One way scientists use flies in this research is to create flies with human disease genes and then observe what happens to the flies. For example, in March 2000, Dr. Welcome Bender of Harvard University and Dr. Mel Feany of Brigham and Women's Hospital engineered flies with Parkinson's disease, the second most common neurodegenerative disorder in humans. The scientists gave the flies a human gene that provides brain cells with instructions for making a protein called alpha-synuclein. When this gene malfunctions in humans, the protein piles up in brain cells. The scientists discovered that--just like people with Parkinson's disease--flies with the human gene have trouble controlling their movements. The flies also have lots of extra alpha-synuclein in their brain cells. By studying these flies, researchers hope to be able to determine the link between the alpha-synuclein gene and brain degeneration. Scientists should also be able to use fruit flies to identify potential new drugs to treat Parkinson's disease.

For decades, scientists have also studied fly brains to figure out why flies--like humans--have daily cycles of activity and night-time rest, known as circadian rhythms. In the 1970s, Dr. Jeffrey Hall of Brandeis University and Dr. Michael Young of The Rockefeller University discovered that a gene called *period* is the internal alarm clock controlling flies' activity and rest cycles. Since then, scientists have identified many other fly genes that affect circadian rhythms, including a gene recently discovered by Dr. Michael Rosbash of Brandeis University, called *take-out*, that may determine when during the day a fly gets hungry. Humans have *period* genes and many--perhaps all--of the other genes that affect flies' daily cycles. By continuing to study circadian rhythm genes in flies, researchers are likely to gain a better understanding of human maladies such as insomnia, jet lag, and perhaps even eating disorders.

Although scientists studying fruit flies have made impressive strides in understanding development, disease, and behavior, much more work lies ahead. Fortunately, future researchers can look forward to an easier time of figuring out what the thousands of newly identified fruit fly genes do. After nearly two decades of groundwork laid by fruit fly researchers, Dr. Kent Golic of the University of Utah finally succeeded in June 2000 in "knocking out" genes in flies, a technique in which researchers get rid of a working gene to see what happens when it is gone. This technical breakthrough is expected to fuel a dramatic increase in knowledge about fly and human genes.

Science Advances

Some of the major research advances made recently with NIGMS support are described below. Although only the lead scientists are named, coworkers contributed significantly to these achievements.

New Insights into Biological Processes

Molecular Structure of Ribosomes Revealed

Ribosomes are the cellular components that manufacture enzymes, hormones, antibodies, and all other proteins in every organism from bacteria to humans. Compared to many other cellular components, ribosomes are large and complex. Each is composed of two subunits and contains genetic material (ribosomal RNA) and more than 50 different proteins. For more than 30 years, scientists have tried to uncover the ribosome's molecular secrets by deciphering its three-dimensional structure.

Now, three research groups led by long-time NIGMS grantees have determined the detailed structures of the ribosome's two subunits. Each group published an initial structure in 1999 and a more refined structure in 2000. Two of the groups focused on the small subunit, which is responsible for translating the genetic message into amino acids, the building blocks of proteins.

These groups are led by Dr. Ada Yonath of the Weizmann Institute of Science in Israel and Dr. Venkatraman Ramakrishnan of the Medical Research Council's Laboratory of Molecular Biology in England. Another team, led by Dr. Thomas Steitz and Dr. Peter Moore of Yale University, studied the large subunit, which links the amino acids into a protein chain.

The structure of the large ribosomal subunit proved a theory that was initially counterintuitive and controversial--that it is the genetic material (the RNA), rather than the proteins, that is responsible for a ribosome's biochemical action.

Ribosome research also sheds light on how antibiotics work. This is because many of today's antibiotics act by interfering with the function of ribosomes in harmful bacteria. To examine at a molecular level how the drugs work, the scientists determined the structure of several antibiotic drugs bound to ribosomal subunits. These studies may help scientists develop new antibiotic drugs or improve existing ones.

Robots Eavesdrop on Cellular Discussions

Imagine visiting a library full of books that you couldn't read. In a sense, this is the scientific dilemma facing biologists across the globe. Researchers have in hand boatloads of genetic information--billions of DNA letters that spell out the instructions for life in organisms as diverse as yeast, worms, flies, and humans. The problem is that, to a great degree, no one knows what all these genes do. And even in the cases where scientists do know, they are still puzzled by how cell parts communicate with each other, often through physical contact. While scientists have developed powerful approaches to determine which of the thousands of genes are "turned on" in a particular cell, they haven't had a "guidebook" to tell them which gene products interact physically.

For the first time, researchers working with the model organism *Saccharomyces cerevisiae* (baker's yeast) have figured out a way to record the "conversations" taking place simultaneously between thousands of molecules inside a single cell. Using robots to monitor the goings-on of thousands of individual yeast cells growing on a small plastic grid, Dr. Stanley Fields of the University of Washington and postdoctoral fellow Dr. Peter Uetz have reached a research milestone in determining which molecules in a cell "talk" to others by making physical contact. To achieve this feat, the researchers used robotic devices to automate state-of-the-art, but common, molecular biological techniques.

"Listening in" on which proteins physically talk to other proteins is a critical task for researchers, since all cells rely on extensive and ongoing molecular discussions to carry out life's functions– everything from breathing to memory. When the complete, ordered sequence of the human genome is available to researchers in the next couple of years, a similar strategy will likely be possible using human cells. In the near term, scientists all over the world studying yeast cells as a model for understanding human health and disease will be able to use this information to advance their research.

Basic Studies Illuminate Disease Mechanisms

Herpes Virus Hijacks Cell's Transportation System

Herpes is a major cause of infectious corneal blindness as well as a host of other diseases, ranging from the common cold sore to life-threatening brain inflammation. The disease is especially dangerous for infants and those with weakened immune systems. Symptoms include itching or burning skin at the infection site and blisters that become painful, oozing sores. After several days, the sores crust over and heal without leaving a scar. After the initial attack, the virus moves to nerve cells and remains there until it is set off again by a variety of factors, including fever, sun exposure, stress, and menstruation.

Scientists already know that the herpes virus finds its way from the nerve ending to the nerve cell body. This movement is critical for the virus to become dormant and to cause future flare-ups. A recent study suggests how the virus manages this directed movement. Dr. Elaine Bearer of Brown University and her colleagues conducted the study by injecting the herpes virus into the giant nerve cells of a squid. These squid cells are frequently used for such research because they are enormous--7 centimeters (2.75 inches) long and almost a millimeter wide--about the size of a small, straightened-out paper clip. The scientists marked the virus particles with a fluorescent protein and used a microscope and a digital camera to track the glowing virus as it moved up the giant nerve cell. The virus moved in one direction, and it traveled at the same constant speed that structures called organelles move within cells. The researchers concluded that the virus usurps the nerve cells' own internal transport machinery.

Other research shows that herpes moves in the same direction and speed in rat nerve cells in culture. Together, these studies strongly suggest that the virus plays the same trick in humans. Understanding how the virus travels within nerve cells may lead to new treatments and perhaps cures for herpes infections. The work not only teaches us about herpes, but also about how normal cellular transport works.

A New Role for Prions

For good reason, a poorly understood group of proteins called prions has gained a notorious reputation in recent years. These proteins have been implicated in a variety of serious brain-destroying diseases, perhaps the most famous of which is Creutzfeldt-Jakob disease, the human version of so-called "mad cow" disease. Despite a substantial amount of research into how prions cause disease, scientists remain puzzled as to what normal functions, if any, prions may participate in within a cell.

To learn more about prion function, researchers have been studying prions in yeast cells. Yeast prions are different from the prions that cause mammalian diseases, and they do not pose any health threat. But yeast prions replicate in the same, very unusual way that mammalian prions do:

They have the uncanny ability to change their shape and cause a chain reaction that makes other proteins of the same type change their shape, too. In the case of prions in mammals, this is associated with a deadly disease, but the yeast prion simply changes the accuracy of protein synthesis.

Dr. Susan Lindquist of the University of Chicago has now discovered a new and unexpected "normal" role for prions: They may help to shape the course of evolution. Dr. Lindquist and postdoctoral fellow Dr. Heather True grew prion-containing yeast cells in 150 different conditions--varying temperature, nutrient source, and other factors, such as the presence of antibiotics or other chemicals. Remarkably, in each of seven different yeast strains the scientists tested, the prion produced a completely different set of growth properties. This means that the cells had been stockpiling genetic changes that went completely unnoticed until the prion turned them on. Dr. Lindquist reasons that in the presence of prions, the increased diversity of a cell's protein repertoire may offer the cell a means to deal with ever-changing environmental conditions, all without affecting DNA and altering the genetic code.

Yeast cells are cheaper and easier to work with than mammals are. Dr. Lindquist's studies in yeast therefore promise to provide new insights into how prion proteins change their shape and function. This knowledge could help researchers devise ways to treat, and perhaps prevent, prion-related neurodegenerative diseases in mammals. The work may also help scientists answer questions about how evolution takes place--in spurts or in a more gradual manner.

New Approaches to Therapeutics

Chemists Improve Synthesis of Anticancer Agent

Approximately 8,100 Americans will develop soft tissue sarcomas--tumors of the muscles, tendons, and supportive tissues--during the year 2000.* These cancers typically require surgery and radiation treatment. Chemotherapy is not a frontline treatment for most soft-tissue sarcomas because a substantial portion of those who are treated with chemotherapy agents experience a relapse of the cancer. Worse still, the returning cancer is often impervious to the chemotherapy drugs.

Dr. Elias J. Corey of Harvard University, the 1990 Nobel laureate in chemistry, may change that. He has improved the synthesis of ecteinascidin, a potent antitumor agent roughly 100 times more powerful than Taxol®, a leading anticancer drug. Although ecteinascidin was discovered in 1988, it has not been widely available because it had to be purified from its natural source, a marine organism, where it exists in tiny quantities. Dr. Corey's new synthesis makes commercial-scale production possible.

**Questions and Answers About Soft Tissue Sarcoma*. National Cancer Institute, 2000.

Ecteinascidin is in Phase II clinical trials and has shown the ability to shrink drug-resistant soft tissue sarcomas. In addition, it may inhibit drug resistance in other forms of cancer. Other researchers have shown that ecteinascidin prevents the formation of P-glycoprotein, a protein associated with multidrug-resistant tumors. P-glycoprotein transports toxins such as chemotherapy drugs out of cancer cells, thereby preventing the drugs from destroying the tumor. Ecteinascidin stops cells from forming more P-glycoprotein, eliminating one of the cancer cells' best defenses against chemotherapy agents.

If its clinical trials are successful and it is eventually approved by the U.S. Food and Drug Administration, ecteinascidin would be the only drug available to treat those sarcoma patients in whom a prior round of chemotherapy had failed. Additionally, by preventing the formation of P-glycoprotein, ecteinascidin may keep other types of tumor cells vulnerable to chemotherapy. Even if ecteinascidin is not proven to be effective on its own, it may become a key ingredient in chemotherapy "cocktails" to prevent tumors from developing resistance to existing anticancer drugs.

Synthetic Antibacterial Molecule Kills Drug-Resistant Bacteria

Many previously treatable bacterial diseases have re-emerged with a vengeance, largely immune to penicillin and its close relatives. Drug-resistant bacteria are now a global health threat. A June 2000 World Health Organization report entitled *Overcoming Antimicrobial Resistance* stated that the growing resistance of major infectious organisms had reduced the healing power of "once life-saving medicines" to that of "a sugar pill." The report highlighted several serious consequences, including an estimated 14,000 deaths in the United States each year from hospital-acquired, drug-resistant infections. As bacteria continue to evade existing therapies, scientists race to stay ahead by developing new antibiotic drugs.

In a promising new approach to antibiotic development, Dr. Samuel Gellman and his coworkers at the University of Wisconsin, Madison have created a synthetic antibiotic molecule out of non-natural forms of amino acids called beta-amino acids. This so-called "beta-peptide" mimics a class of natural antimicrobial molecules called magainins. These molecules exist in a wide variety of forms in nature and defend biological borders, such as skin, from invading bacteria. The beta-peptide has shown its antibiotic properties in the lab, killing both normal and drug-resistant strains of infectious bacteria, including a strain resistant to vancomycin, the "last resort" antibiotic that must be administered intravenously in a hospital.

The beta-peptide has two promising characteristics that distinguish it from traditional antibiotics. In combination, these two factors could be enough to prevent bacteria from developing resistance. First, researchers believe that bacteria may have trouble developing resistance to the beta-peptide because bacterial defenses may not recognize its non-natural amino acids. Second, the magainins that the beta-peptide mimics have been around for millions of years, yet bacteria have not become resistant to them.

The beta-peptide must undergo further testing in the form of animal and clinical studies before its usefulness as a drug is known. But even if the beta-peptide never becomes a drug, this research shows that it is possible to design from scratch the structure of a protein with a desired biological action.

Targeted DNA Insertion May Aid Gene Therapy

For decades, scientists have tried to insert genes into precise locations within the genetic material of laboratory test organisms. Such experiments help them better understand the function of the inserted genes and enable them to disrupt other genes under study. The concept of human gene therapy also relies on the insertion of corrective genes into cells. With most current methods, however, the genes insert randomly, so scientists cannot control whether the genes will function in their new location. Such random insertions can even lead to potentially disease-causing mutations.

New research indicates that it is possible to insert genes into any desired location in the genetic material of a host organism. Dr. Alan Lambowitz of the University of Texas, Austin and his coworkers accomplished this by harnessing the targeting mechanism of a portion of DNA called an intron. Introns normally do not code for proteins, but exist in the middle of genes that do. Some introns can recognize a sequence of DNA and insert themselves precisely into it. They do this by matching up a region of their own genetic sequence with the targeted sequence. To see whether it is possible to construct introns to target any desired gene, the researchers chose two clinically relevant sequences to target: one in a gene in HIV, the virus that causes AIDS, and another in a human gene called CCR5 that encodes a protein necessary for HIV infection. People who have mutations in their CCR5 genes are resistant to HIV infection, and so some scientists believe that disrupting the CCR5 gene may be an effective anti-AIDS therapy. Dr. Lambowitz's group modified a type of intron found in bacteria to generate a variety of introns with different genetic sequences in their targeting regions. The scientists found that more than a dozen of these introns inserted themselves into the intended positions in the target genes. Dr. Lambowitz's group experimented on human cells in a laboratory, but the scientists hope the technique ultimately can be used to treat HIV infection in people.

If further tests are successful, the method could advance all sorts of biomedical research, ranging from studies on basic gene function to the development of antiviral and antibacterial drugs. The work may also enhance the delivery of genes for gene therapy. This is an excellent example of an unexpected outcome from basic biomedical research. "We were carrying out basic research on [these] introns and how they related to gene structure," said Dr. Lambowitz. "Any kind of practical application was the furthest thing from our minds."

Simple Breath Test Predicts Gene-Linked Response to Medicine

Pharmacogenetics is the blossoming area of research that connects a person's genetic make-up with his or her response to medicines. As medicines move through the body, they interact with thousands of proteins, each encoded by a different gene. Some of these proteins work to get rid of medicines, while others help medicines do their jobs. Because each person is genetically

unique, tiny differences in these proteins can affect how medicines act in the body. For example, certain drugs used to treat cancer can have widely variable effects in patients, and many of these treatments have serious toxicities. On occasion, patients are literally poisoned because their bodies cannot get rid of, or "clear," cancer treatments in a timely manner. Patients given an identical dose of the commonly used chemotherapy drug Taxotere® (docetaxel), for instance, display wide variations in the amount of time it takes their bodies to clear this medicine. Scientists have suspected that gene differences may account for at least some of the variability in response to docetaxel.

Now, Dr. Paul Watkins of the University of North Carolina, Chapel Hill has confirmed this suspicion using a simple "breath test" that measures an individual patient's ability to break down docetaxel. Several years ago, Dr. Watkins and his coworkers came up with the idea for the breath test, which measures the strength of a drug-metabolizing protein with the not-so-catchy nickname of "CYP3A4." The CYP3A4 protein chews up many different drugs, including the antibiotic erythromycin. Researchers use the breath test to gauge a patient's CYP3A4 activity by injecting a tiny amount of erythromycin containing trace levels of a radioisotope of carbon and then measuring the amount of radioactive carbon dioxide the patient exhales 20 minutes later. (The very small amount of radioactivity poses no danger to the patient or the health care provider.) In a small clinical study, Dr. Watkins and his team successfully used the breath test to track patients' breakdown of docetaxel. Underscoring the predictive value of the simple test, the scientists found that the patients with the lowest scores on the breath test were the ones who suffered the greatest docetaxel toxicity.

Dr. Watkins' new work introduces an important potential role for the breath test in predicting toxicity caused by a widely used cancer drug. Because many medicines are metabolized by the CYP3A4 protein, the breath test may prove useful in the clinic as a rapid and easy way to predict individual patients' responses to other drugs. Since previous blood tests failed to predict docetaxel toxicity ahead of time, the breath test may offer a promising tool to help doctors administer this drug more safely. Makers of the breath test are currently seeking U.S. Food and Drug Administration approval--a step that would mark another practical use of pharmacogenetics in the clinic.

Living Skin Grafts Enhance Burn Treatment

In the United States, 1.25 million people seek medical attention for burns every year, according to the American Burn Association.* Third-degree burns, which extend to the deepest of the skin's layers, require immediate care to prevent infection and dangerous fluid loss that can lead to shock. A quarter-century ago, NIGMS-funded burn surgeons determined that badly burned skin should be removed as quickly as possible (rather than letting it slough off over time), followed by immediate and permanent replacement of the lost skin. This seemingly simple idea ultimately became standard practice for treating major burn injuries and led to the development of what is now an artificial skin system called Integra® Dermal Regeneration Template™. After removing the damaged skin, surgeons blanket a burn wound with a covering like Integra®, then apply a skin

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**Burn Incidence and Treatment in the United States.* American Burn Association, 1999.

graft on top of this biomaterial to coax the growth of new skin to close the wound. Ideally, surgeons obtain skingrafts from the burned patient, but in the case of severe burns covering 80 to 90 percent of the body surface, there is not enough remaining skin to use for this purpose.

Dr. Steven T. Boyce of the University of Cincinnati and the Cincinnati Shriner's Burns Hospital has now succeeded in growing skin cells from a burned patient and adding them to a polymer sheet to create living skin grafts in the laboratory. In an effort to permanently close burn wounds, Dr. Boyce and his coworkers placed the laboratory-grown skin grafts on top of Integra® and bathed everything with a nutritious mix of growth factors and antibiotics to help prod the growth of new blood vessels and control infection. The researchers tested this technique on three children who had been badly burned in fires. The results were promising, showing that the new method offers an advantage over other currently available technologies, such as using non-living skin substitutes that cannot as accurately restore the structure and function of native skin. In each test case, the patient's new skin was a lighter color than before, but it returned to its original softness, smoothness, and strength with minimal scarring.

The new method may improve the treatment of severely burned patients who have lost more than half of their skin to third-degree burns, because the lack of available skin for grafting the burn wounds of these patients often limits recovery. This approach to wound treatment may also decrease treatment costs and hospitalization times associated with the treatment of severe burns, although more studies are needed to formally test these predictions. Finally, the method restored much of the cosmetic appearance of the burn-damaged skin of these young patients--a crucial element in helping burn patients return to a normal life.

New Activities

Structural Genomics

As described earlier in this narrative, the success of genome sequencing projects and recent advances in protein structure determination techniques have ushered in a new field, called structural genomics, that is focused on the large-scale analysis of protein structures based on gene sequences. To stimulate this field and capitalize on the opportunities it presents, NIGMS created a Protein Structure Initiative designed to organize a large, cooperative effort in structural genomics.

Through the initiative, NIGMS seeks to develop a public database of protein structures. This database will link sequence, structural, and functional information and will allow scientists to use gene sequences to predict the structures of many other proteins.

The Protein Structure Initiative supports technology development by researchers and small businesses. It also supports pilot research centers to develop high-throughput tools and strategies for every aspect of structural genomics, from the selection of proteins for structure determination to analyzing the final data. In September 2000, NIGMS awarded $29.7 million to fund the first year of seven pilot research center projects, each of which will be funded for 5 years. (An

additional $1.5 million in funding for one of the research centers was provided by the National Institute of Allergy and Infectious Diseases.) Other countries are launching structural genomics programs, and NIGMS--the world's single largest funder of structural genomics--is leading the U.S. effort.

Pharmacogenetics

Diet, environment, and lifestyle can all influence how a person responds to medicines--but another key factor is genes. NIGMS and five other NIH components are sponsoring a nationwide research effort to understand how a person's genetic make-up determines the way a medicine works in his or her body, as well as what side effects the person might be prone to developing. This field of research, called pharmacogenetics, focuses on linking the body's response to medicines with variations in particular genes. Through these types of studies, researchers ultimately hope to develop drug dosing into a much more predictive science.

The trans-NIH effort, which is being led by NIGMS, has forged an interactive research network of investigators who will store data in a shared information library that is freely accessible to the scientific community. To protect participants' privacy, names and other identifying information will not be stored in this library. The first nine pharmacogenetics research network awards– totaling $12.8 million for the first year of funding, $8.5 million of it from NIGMS--were made in April 2000. The network is forming an industry liaison group to serve as a forum for identifying and discussing interests and goals shared by network scientists and the pharmaceutical industry.

"Glue" Grants

Leaders in the scientific community have advised NIGMS that the thorniest biological problems require the expertise and input of large, multifaceted groups of scientists. In response to this input, NIGMS created a research initiative to "glue" together large groups of scientists pursuing some of the biggest unsolved problems in biomedicine today. In September 2000, NIGMS made the first "glue" grant award of $7.3 million for the first of 5 years to a consortium of basic scientists called the Alliance for Cellular Signaling. (An additional $1.5 million in funding came from the National Institute of Allergy and Infectious Diseases.) The Alliance is led by Nobel laureate Dr. Alfred Gilman of the University of Texas Southwestern Medical Center at Dallas, and it includes 50 scientists at 20 institutions plus 250 more auxiliary members. Alliance scientists will study all aspects of cellular communication in two cell types: cardiomyocytes (heart muscle cells that can beat in a dish) and B-cells (immune cells that move around the bloodstream carrying out duties for the body). A key goal of the effort is to map the vast number of signals that course through these cells. Alliance scientists hope to create a piece of a virtual cell, which could enable drug developers to test new compounds *"in silico,"* meaning that they will have the ability to search for new drugs using a computer alone.

Integrative Research and Studies of Complex Biological Systems

Historically, biomedical researchers have sought to understand basic life processes by studying the individual components of biological systems. But now, researchers like Dr. Gilman and his Alliance for Cellular Signaling increasingly are taking a more integrative view of how cells, tissues, and whole organisms function. Integrative studies might seek to understand all of the genetic and environmental components that work together to regulate processes such as inflammation and metabolism, traits like height and blood pressure, and complex conditions such as diabetes and heart disease. NIGMS has established programs to stimulate integrative research as well as research on complex biological systems. It is also recruiting mathematicians, physicists, engineers, and computer scientists to this area of biomedical research.

Biocomputing and Bioinformatics

As biomedical research--particularly integrative research and research on complex biological systems--generates more and more data, the need for scientists with expertise in biocomputing and bioinformatics is increasing dramatically. To train more scientists in these fields, NIGMS currently offers a predoctoral training program in bioinformatics and computational biology. The program is designed to support training in the background theory and biological application of the information sciences--including computer science, statistics, and mathematics--to biomedical research problems.

The Institute is planning several additional biocomputing and bioinformatics activities, including: Centers of Excellence in Biocomputing and Bioinformatics, model systems for computational biology, institutional postdoctoral training grants in bioinformatics and computational biology, a joint National Science Foundation/NIGMS program to support research in mathematical biology, and a "generic" model organism database.

All of these efforts respond to pressing needs in the scientific community that NIGMS is taking a leadership role in addressing. An example is the model organism database. Existing model organism databases do not have consistent formats that promote accessibility and interaction among scientists studying various model organisms, and the creation of databases for additional model organisms is likely to exacerbate the problem. A "generic" model organism database would serve as a framework for new databases, making their development more cost-effective. It would also enable researchers to obtain data about different organisms more efficiently, which will enhance their ability to make the comparisons between organisms that are so critical to advancing understanding of fundamental biological processes.

Health Disparities

NIGMS recently began a collaboration with the Indian Health Service to improve and expand health research involving American Indian and Alaska Native tribes and people. The goal of this collaboration is to enhance the capacity and skills of tribal organizations and Native American researchers to conduct high-quality biomedical and behavioral health research and to apply successfully for competitive research grants.

The pharmacogenetics research initiative described above will likely reveal new information linking differences in response to medicines with genes that are more common in certain population groups. Such knowledge could contribute to a reduction in health disparities by improving doctors' ability to identify and treat individuals who have these genes. Beyond these general benefits, NIGMS is planning to offer research grant supplements in FY 2001 for studies that are specifically related to health disparities in response to medicines.

Another proposed NIGMS health disparities activity would focus on differences between various population groups in the physiological response to traumatic injury. New information about such differences could improve doctors' ability to anticipate how trauma patients are likely to fare, especially which patients are at higher risk of developing the potentially fatal--and currently unpredictable--systemic inflammatory response syndrome.

Details on these and other NIGMS plans for reducing health disparities are posted on the NIGMS Web site at http://www.nigms.nih.gov/news/reports/health_disparities.html.

Other Areas of Interest

Research Grants

NIGMS has continued the efforts it started several years ago to help balance the need for stability in the research community with the need to respond to new scientific opportunities. FY 2000 was the fourth year in which NIGMS provided interim funding at a reduced level to investigators whose competing continuation applications for regular research grants were just beyond the Institute's funding range. This support has helped productive laboratories avoid the loss of momentum, staff, and resources caused by lapses in funding. During FY 2000, NIGMS made 59 interim awards for a total of $4.11 million.

NIGMS maintained its commitment to support adequate numbers of new investigators by funding 189 applications in FY 2000 from investigators who previously had no independent research grant support from NIH. Of those, 25 were beyond the Institute's payline and were funded as a result of its efforts to support new investigators.

The NIGMS program to support "high-risk/high-impact" research proposals funded 51 awards totaling $5.49 million in FY 2000. The proposals are "high-impact" because they have the potential for groundbreaking, precedent-setting significance; they are "high-risk" because they either lack sufficient preliminary data to ensure their feasibility or they involve using new model systems or techniques. Interestingly, one of the scientists featured in the fruit fly story of discovery earlier in this document, Dr. Kent Golic, did his breakthrough work with support from the NIGMS "high-risk/high-impact" program. Although the fly research community was eager to be able to use gene knockout technology, no one before Dr. Golic was willing to take the risk of applying for funding for a project with such an uncertain chance of success.

Another study that was partially supported by the "high risk/high impact" program is leading scientists to rethink the cause and treatment of rheumatoid arthritis. It was long thought that this condition is the result of an overactive immune system, but research by Dr. Jorg Goronzy and his colleagues at the Mayo Clinic in Rochester, Minnesota suggests that this form of arthritis may instead be due to premature aging of the immune system. If further studies bear out this finding, current rheumatoid arthritis treatments that suppress the immune system would need to be changed.

Also in FY 2000, the Institute announced a new supplement program to enable scientists holding NIGMS-funded research grants to obtain resources for DNA microarray expression analysis directly related to the aims of the parent grant. The microarray is a revolutionary new tool that enables scientists to take a "snapshot" of gene expression in a cell so they can see all of the genes that are active or inactive under various conditions. This is a one-time supplement program that will provide a maximum of $50,000 per grant; in the future, NIGMS grant applicants and current grantees will be expected to include microarray costs in their new or renewal applications. NIGMS intends to spend up to $5 million on this program in FY 2001.

Research Training

NIGMS maintains its leading role at NIH in research training by supporting nearly half of the predoctoral trainees and approximately 27 percent of all of the trainees who receive assistance from NIH. In recognition of the interdisciplinary nature of biomedical research today, the Institute's research training programs stress approaches to biological problems that cut across disciplinary and departmental lines. Such experience prepares trainees to pursue creative research careers in a wide variety of areas.

One special program, the Medical Scientist Training Program (MSTP), supports research 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 response to the pressing need for more investigators with such training, in FY 1999 NIGMS expanded the number of trainees in this program from 828 to 890, and in FY 2000, it expanded the number of trainees again, to 911. Another program, the Pharmacology Research Associate (PRAT) Program, is NIGMS' only intramural activity. The goal of this program is to develop top-flight leaders in pharmacological research who will take key positions in academic, industrial, and government research laboratories. PRAT fellows conduct 2 years of postdoctoral research in NIH intramural laboratories, working in such cutting-edge research areas as neurobiology, neurochemistry, tumor biology, and cellular signaling systems.

In FY 2000, NIGMS received applications in response to a new program to support summer research experiences for undergraduate students. The program will provide opportunities for students in the quantitative and physical sciences--including engineering, mathematics, computer science, and physics--to take part in mentored biomedical research experiences with NIH-supported investigators. The first awards under this program will be made in FY 2001.

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 regular research grants focused on improving the understanding of AIDS and its associated opportunistic infections.

NIGMS initiated its AIDS-related program project grants in 1987 to bring together crystallographers, chemists, and biologists to determine the detailed, three-dimensional structures of potential drug targets in HIV.

The NIGMS research training program in molecular biophysics, which was established in 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 within the Institute 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. Support is available at the undergraduate, graduate, postdoctoral, and faculty levels.

The MORE Division has three components: the Minority Biomedical Research Support (MBRS) Branch, the Minority Access to Research Careers (MARC) Branch, and a section that handles special initiatives. Through MORE's programs, NIGMS takes the lead role at NIH in research and research training activities targeted to underrepresented minorities.

In FY 2000, MORE announced a new program designed to encourage underrepresented minorities who hold a recent baccalaureate degree in a biomedically relevant science to pursue a research doctorate. The Post-Baccalaureate Research Education Program (PREP) allows participants to work as apprentice scientists in a preceptor's laboratory and to participate in student development activities. The program is expected to strengthen the research skills and competitiveness of participants for pursuit of a graduate degree, while also stimulating them to have an interest in addressing the health problems that disproportionately affect minorities and the medically underserved in the United States.

Minority Biomedical Research Support Branch

MBRS awards grants to minority-serving institutions (MSIs) through three programs: Support of Continuous Research Excellence (SCORE), Research Initiative for Scientific Enhancement (RISE), and the Initiative for Minority Student Development (IMSD).

The purpose of the SCORE Program is to assist biomedical research faculty at MSIs in developing competitive research programs and to increase the number of underrepresented minorities professionally engaged in biomedical research. The RISE Program seeks to enhance the research environment and increase the interest, skills, and competitiveness of students and faculty in pursuit of biomedical research careers. The IMSD encourages domestic public and private educational institutions with fully developed and funded research programs to initiate and/or expand innovative programs to improve the academic and research capabilities of underrepresented minority students and to facilitate their progress toward careers in biomedical research.

MBRS awards also support student and faculty developmental activities identified by the applicant institution, including attendance at scientific meetings and workshops, special activities such as novel classes and curriculum changes, and participation in research at on- and off-campus laboratories. In FY 2000, 499 faculty members at 106 institutions worked on 368 MBRS research projects, and 1,207 undergraduate and 829 graduate students participated in these projects as research assistants.

Minority Access to Research Careers Branch

MARC supports special research training opportunities for students and faculty at educational institutions with substantial minority enrollments. MARC programs also enable grantee institutions to develop and 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 accomplishes these goals through Undergraduate Student Training in Academic Research (U*STAR) institutional grants, predoctoral fellowships, faculty predoctoral and senior fellowships, a visiting scientist program, and grants for MARC ancillary training activities.

MARC support in FY 2000 went to 644 students at 62 institutions that participated in the undergraduate program, 29 students who received MARC predoctoral fellowships, and 4 faculty members who received training and/or degrees through the faculty fellowship program.

MARC also supports a program of NIH predoctoral fellowships for minorities. The Branch has awarded 75 of these fellowships, 32 of which were new in FY 2000.

Special Initiatives Branch

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 Office of Research on Minority Health. 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) toward careers in biomedical research. Since the inception of the Bridges Program in 1992, NIGMS has supported 118 programs, 14 of which received initial funding in FY 2000.

The division also supports the MORE Faculty Development Award. This 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. In FY 2000, five individuals received these awards.

In FY 2000, the division funded four grants under the Institutional Research and Academic Career Development Award, an innovative program that combines a traditional mentored postdoctoral research experience with an opportunity to develop teaching skills through mentored assignments at an MSI. The goals of the program are to provide a resource to motivate the next generation of scientists at MSIs and to promote linkages between research-intensive institutions and MSIs that can lead to further collaborations in research and teaching. The program offers a broader-
than-usual training experience to postdoctoral scientists. According to one of the grant recipients, "The postdoc will develop people and productivity skills for the workplace that translate into broader, more diverse marketability; the research university will receive added research skills and support for its academic research programs; the [MSI] will bring instruction and research opportunities to its students in specialties not available on its campus; and the science community will get a professional prepared to contribute to the profession through a greater variety of career paths."

An activity that continued to be a success in FY 2000 is the MORE Division's support of technical assistance workshops and mini-courses in a number of areas, including grant writing and program evaluation. The University of Kentucky sponsored an online technical assistance workshop on grant writing that offered the equivalent of a 6- to 10-week graduate-level course using interactive Internet technologies. The American Physiological Society continued hosting a course aimed at assisting MARC and MBRS program directors in developing and implementing effective evaluation programs. The Federation of American Societies for Experimental Biology sponsored two grant-writing seminars aimed at providing investigators with the skills necessary to prepare a successful grant application.

The NIGMS collaboration with the Indian Health Service mentioned earlier is an activity of the MORE Division. This program, called Native American Research Centers for Health (NARCH), will promote, develop, and support centers that link the Native American community with organizations that conduct health research. It will also encourage research on diseases and health conditions of importance to American Indians and Alaska Natives. In addition, the NARCH Program seeks to develop a cadre of Native American biomedical and behavioral scientists and health professionals who are able to compete successfully for NIH funding. At the same time, it aims to increase the capacity of both the research-intensive organizations and the Native American organizations to work in partnership to produce competitive research proposals. The program will provide funds to support faculty-initiated, scientifically meritorious research projects, including pilot research projects, at NARCH organizations. It will also support projects designed to increase the research skills and number of Native American science students.

Success Stories

In FY 2000, participants in MORE programs continued to receive national attention for their research. For example, Joseph L. Nunez, a MARC predoctoral fellow at the University of Illinois, published an article in the March 2000 issue of *Developmental Brain Research*. Mr. Nunez's study provided evidence that portions of the brain continue to develop well past puberty, which contradicted conventional thinking that brain development ended in early childhood. The research, which was conducted on rat brains, offered some of the clearest experimental evidence to date showing brain development continuing well into early adulthood.

Reflecting their exceptional achievements in nurturing students who are interested in careers in science, four MORE program directors were among the ten individual recipients of this year's Presidential Awards for Excellence in Science, Mathematics and Engineering Mentoring. They are:

- Dr. Glenn Kuehn, New Mexico State University, Las Cruces;
- Dr. Michael Summers, University of Maryland, Baltimore County;
- Dr. Luis Villarreal, University of California, Irvine; and
- Dr. Maria Elena Zavala, California State University, Northridge.

Many participants in MORE programs go on to productive academic careers and professions in research or research administration. This provides evidence that the educational strategy of involving students in hands-on research experiences is one that works. Among this year's "success stories" are:

- Dr. Kristine Garza, a former MARC undergraduate student at St. Mary's University in San Antonio, Texas, is now an assistant professor in the department of biological sciences at the University of Texas at El Paso.
- Dr. Wilfred Denetclaw, a former MBRS program participant at Diné College in Shiprock, New Mexico and a former MARC trainee at Fort Lewis College in Durango, Colorado, is now an assistant research cell biologist at the University of California, San Francisco.
- Ryan and Bryan Turner, identical twin brothers and former MARC trainees at the University of Maryland, Baltimore County, are second-year M.D.-Ph.D. students at Harvard University.

Innovations in Management and Administration

NIGMS places great emphasis on innovation, foresight, and continuous improvement in its management and administration. Some of the Institute's recent activities in these areas are described below.

Administrative Retreats

Several years ago, the Arthur Andersen consulting firm recommended that NIH forge a closer partnership between its administrative management functions and its scientific programs. As part of a response to this recommendation, NIGMS teamed up with the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke to hold three administrative retreats. The goal of this effort was to define ways in which the three organizations might share best practices, undertake common problem solving, and discuss approaches to meeting new challenges. Follow-up activities to the retreats included researching best practices for employee recruitment in science-oriented Federal agencies, examining how the organizations might best prepare for adoption of the NIH Business System travel module, and exploring possible ways to evaluate some of the grant program changes that are affecting how NIH staff and grantees operate.

Information Technology Resource Management

Government information technology (IT) mandates, NIH IT initiatives, and NIGMS IT requirements all place ever-increasing demands on the Institute's IT staff and infrastructure. To determine whether it is properly managing its IT functions, NIGMS hired a consulting firm to conduct a study and recommend a management framework and strategies for optimizing Institute IT staffing and resources.

NIGMS also has a staff committee that continues to serve as a forum for the exchange of information and advice between NIGMS staff and the Institute's Information Resources Management Branch. This committee ensures that NIGMS IT activities are grounded in the needs and shared vision of the Institute staff.

Council Information Web Site

In an effort to reduce the volume of paper documents provided to National Advisory General Medical Sciences Council members, as well as to provide them with the most up-to-date information possible, NIGMS created a Council Information Web Site. The site provides electronic access to such items as the meeting agenda, orientation information, and material on current and proposed Institute activities.

E-IMPACT Committee

The NIGMS E-IMPACT committee was established at the start of FY 2000 to examine how a number of impending activities, such as electronic research administration, might affect NIGMS work processes and staffing. The group is developing recommendations that will enable the Institute to plan for and implement the changes anticipated as a result of these activities.

Training Partnership

In September 1999, NIGMS entered into a 1-year pilot partnership with the National Library of Medicine to share the Library's computer software training resources. An evaluation of the pilot confirmed that the partnership was a success and led both parties to enter into another training agreement for FY 2001.

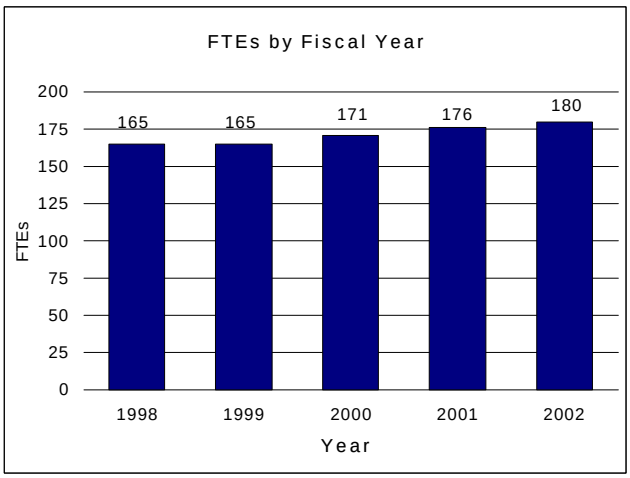
NIH Competitive Service Center Participation

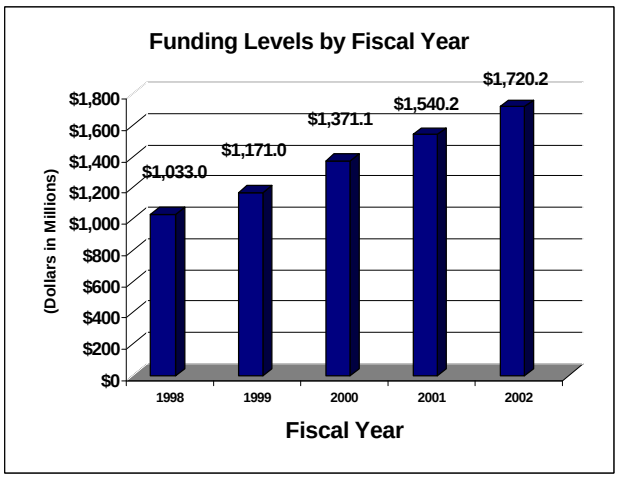
NIGMS continues to be a participant in two NIH competitive service centers. It is a user of the Center for Scientific Review's Scientific Review Evaluation Award Check Writing Competitive Service Center and the National Institute of Child Health and Human Development's Committee Management Competitive Service Center.

NIH Budget Policy

The Fiscal Year 2002 budget request for the NIGMS is $1,720,206,000, including AIDS, an increase of $180,012,000 and 11.7% over the FY 2001 level, and $349,060,000 and 25.5 percent over the FY 2000.

A 5 -year history of FTEs and Funding Levels for NIGMS are shown in the graphs below.





One of NIH's highest priorities 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 Fiscal Year 2002 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4.3 percent. Noncompeting RPGs will receive increases of 3 percent on average for recurring direct costs. In FY 2002, total RPGs funded will be 4,139 awards, an increase of 95 awards over the FY 2001 Estimate, the highest annual total ever awarded.

Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the Fiscal Year 2002 request, NIGMS will support 4,482 pre- and postdoctoral trainees in full-time training positions. An increase of 10 percent over Fiscal Year 2001 levels is provided for stipends and training-related expenses (e.g., health insurance, research supplies and equipment, and travel to scientific meetings).

The Fiscal Year 2002 request includes funding for 32 research centers, 292 other research grants, and 16 R&D contracts.

The Fiscal Year 2002 request includes an increase of $3,920,000 and 11.5% to support research management and support activities. NIGMS has already announced significant research initiatives for FY 2001 that will require both new scientific expertise and grants management stewardship, now and in the future. These activities include Computational Biology, Protein Structure, Pharmacogenetics and Health Disparities. NIGMS just concluded a study of its Information Technology (IT) infrastructure. The study recommended that management positions as well as technology staff positions be filled. With the Institute's grant workload expanding and the NIH enterprise IT environment placing greater demands on the Institute, these staff are essential to NIGMS operations.

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