From Molecules to Medicines

Research and Training Programs of the National Institute of General Medical Sciences

National Institutes of Health
National Institute of General Medical Sciences

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U.S. DEPARTMENT OF
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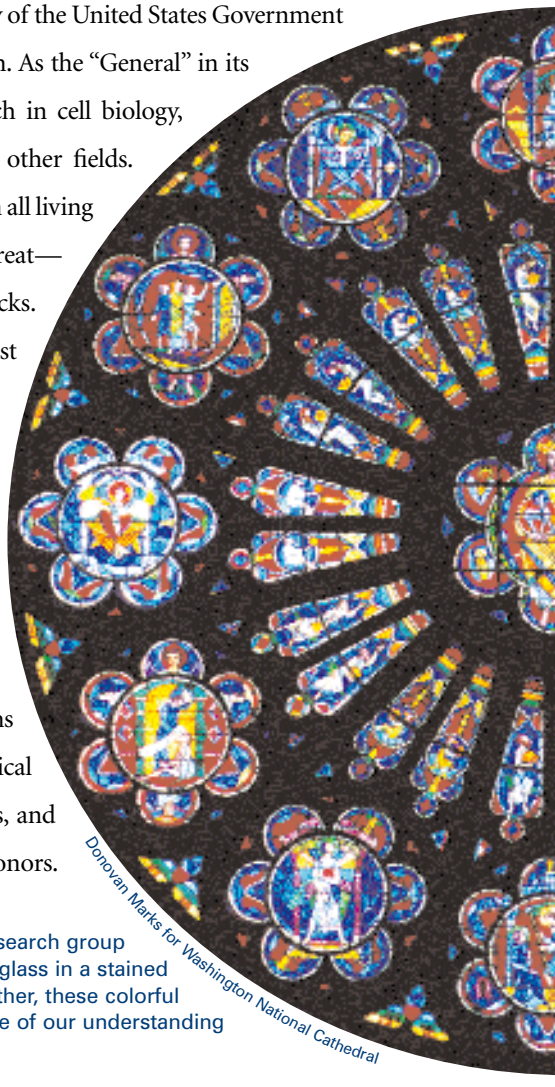
Introduction

Many scientists across the country are united by one chief desire—to improve our understanding of how life works. Whether they gaze at or grind up, create or calculate, model or manipulate, if their work sheds light on living systems, it may well receive financial support from the National Institute of General Medical Sciences (NIGMS).

NIGMS is part of the National Institutes of Health (NIH), an agency of the United States Government that is one of the world's leading supporters of biomedical research. As the "General" in its name implies, NIGMS has broad interests. It funds basic research in cell biology, structural biology, genetics, chemistry, pharmacology, and many other fields. This work teaches us about the molecules, cells, and tissues that form all living creatures. It helps us understand—and possibly find new ways to treat—diseases caused by malfunctions in these biological building blocks. The Institute also supports training programs that provide the most critical element of good research: well-prepared scientists.

Because the NIGMS mission is so wide-ranging, the Institute has one of the largest budgets of all the NIH components. In 2002, the NIGMS budget is over $1.7 billion, and it supports the research of more than 3,000 scientists at universities, medical schools, hospitals, and other research institutions.

NIGMS-funded work has yielded many scientific breakthroughs and contributed substantially to an explosion of progress in biomedical research. Many NIGMS grantees are at the forefront of their fields, and a number have received the Nobel Prize and other high scientific honors.



Donovan Marks for Washington National Cathedral

◆ The contribution of each research group is like one piece of colored glass in a stained glass window. Viewed together, these colorful pieces form a radiant picture of our understanding of living systems.

Supporting and contributing to the work of these leaders are legions of collaborators, postdoctoral fellows, and students. We are not able to include the names of all of those who contributed to the advances featured in this booklet. But without question, today's scientific research would not be possible without the ideas, advice, labor, supplies, and tools of such coworkers.

NIGMS organizes the research it supports into four divisions and one center:

- Division of Cell Biology and Biophysics
- Division of Genetics and Developmental Biology
- Division of Minority Opportunities in Research
- Division of Pharmacology, Physiology, and Biological Chemistry
- Center for Bioinformatics and Computational Biology

The Institute also has a Division of Extramural Activities that is responsible for grant-related activities and policies.

The following pages provide a sampling of the research supported by NIGMS and some of the resulting scientific advances.

To learn more about the science supported by NIGMS and how to become involved yourself as a scientist, a student, or an interested citizen, go to the NIGMS Web site at http://www.nigms.nih.gov.

Alisa Zapp Machalek
Science Writer, NIGMS
May 2002

NIGMS Nobelists

These are a few of the 50-plus NIGMS-supported researchers who have received a Nobel Prize since the Institute was established in 1962.

Nobel Laureate	Prize and Year	Citation
Har Gobind Khorana Robert W. Holley (shared with Marshall W. Nirenberg)	Physiology or Medicine 1968	"For their interpretation of the genetic code and its function in protein synthesis"
Christian de Duve George E. Palade (shared with Albert Claude)	Physiology or Medicine 1974	"For their discoveries concerning the structural and functional organization of the cell"
Daniel Nathans Hamilton O. Smith (shared with Werner Arber)	Physiology or Medicine 1978	"For their discovery of restriction enzymes and their application to problems of molecular genetics"
Sidney Altman Thomas R. Cech	Chemistry 1989	"For their discovery of catalytic properties of RNA"
Elias James Corey	Chemistry 1990	"For his development of the theory and methodology of organic synthesis"
Alfred G. Gilman (shared with Martin Rodbell)	Physiology or Medicine 1994	"For their discovery of G-proteins and the role of these proteins in signal transduction in cells"
Leland H. Hartwell (shared with R. Timothy Hunt and Paul M. Nurse)	Physiology or Medicine 2001	"For their discoveries of key regulators of the cell cycle"
K. Barry Sharpless (shared with William S. Knowles and Ryoji Noyori)	Chemistry 2001	"For his work on chirally catalysed oxidation reactions"

Cell Biology and Biophysics

The Division covers the following areas:

- cell organization, movement, and division
- lipid biochemistry
- membrane structure and function
- biomedical instrumentation
- spectroscopic, analytical, and separation techniques
- molecular biophysics
- structural biology (including the structures of AIDS-related proteins) and structural genomics

Studying Cells and the Molecules Within Them

Research supported by the Division of Cell Biology and Biophysics illuminates the structure and function of cells, cellular components, and the biological molecules—proteins, lipids (fats), and genetic material (DNA and RNA)—that make up these components. The long-term goal of the Division is to find ways to prevent, treat, and cure diseases caused by abnormal cellular activity.

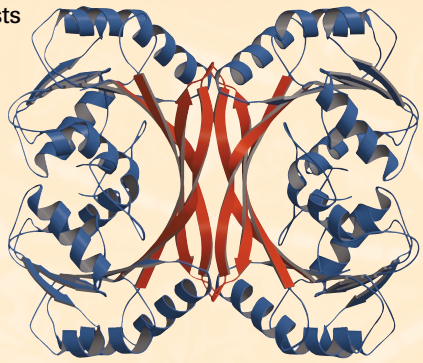
Exploring the Birthplace of Proteins

One way to examine the role of various molecules in health and disease is to decipher and study details of the molecules' three-dimensional structures. For scientists who study such structures, one of the most thrilling moments in recent history came in 1999 when, capping more than 30 years of effort, three groups of NIGMS-supported researchers unveiled the structure of the ribosome—the cellular birthplace of proteins in every living creature.

A Catalog of the Shapes of Life

For several decades, NIGMS has supported scientists who determine the detailed structures of proteins and other molecules. These structural biology studies have shed brilliant light on specific proteins.

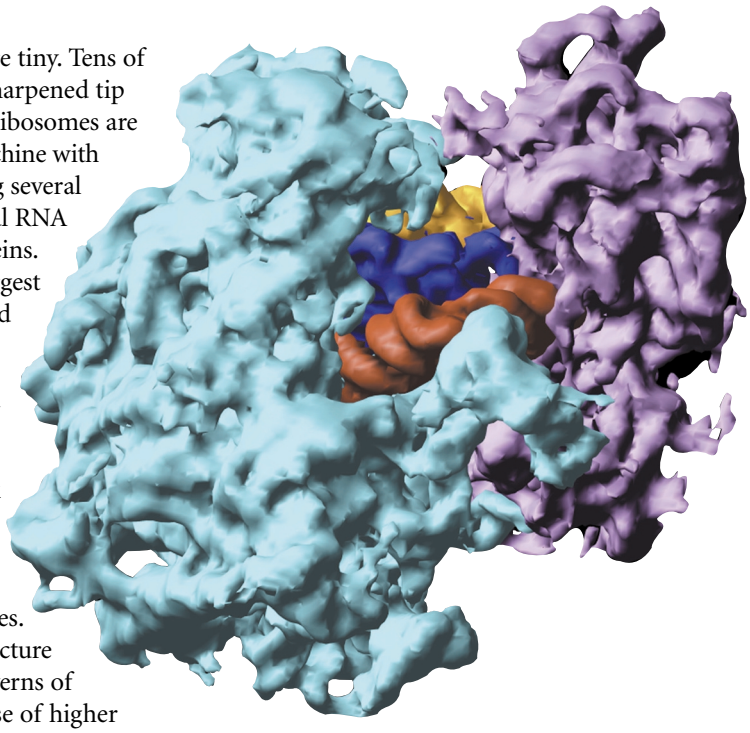
But now, NIGMS has launched an additional, more organized effort in a related field called structural genomics. As its name implies, structural genomics hinges on the relationship between protein structures and gene sequences. (A genome is an organism's complete genetic sequence.) The driving force behind this effort is the desire to forge a "shortcut" to solving protein structures.



- Two of the first molecular structures determined under the NIGMS structural genomics project. The structures held a number of scientific surprises, including structural features never seen before.

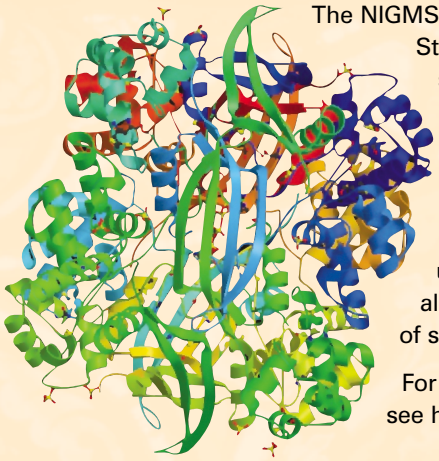
To most people, ribosomes are tiny. Tens of thousands would fit on the sharpened tip of a pencil. But to scientists, ribosomes are huge. Each is a molecular machine with many moving parts, including several strands of the genetic material RNA and more than 50 small proteins. The ribosome is by far the largest molecular complex yet to shed its structural secrets. These secrets include how its many pieces fit together and exactly where proteins are made.

As a spin-off benefit, the work may advance the design of antibiotic drugs. Many of today's antibiotics work by sabotaging bacterial ribosomes. By comparing the overall structure and internal channels and caverns of bacterial ribosomes with those of higher organisms such as humans, researchers may be able to design compounds that clog the works of bacterial ribosomes but leave human ribosomes alone. This could lead to new antibiotics that are highly effective and have minimal side effects.



◆ The first structural snapshot of an entire bacterial ribosome. Detailed studies of this structure will help researchers better understand how proteins are made. They may also lead to new or better antibiotic medicines.

Ribosome structure courtesy of Jamie Cate, Marat Yusupov, Gulnara Yusupova, Thomas Earnest, and Harry Noller. Graphic courtesy of Albion Baucom, University of California, Santa Cruz.

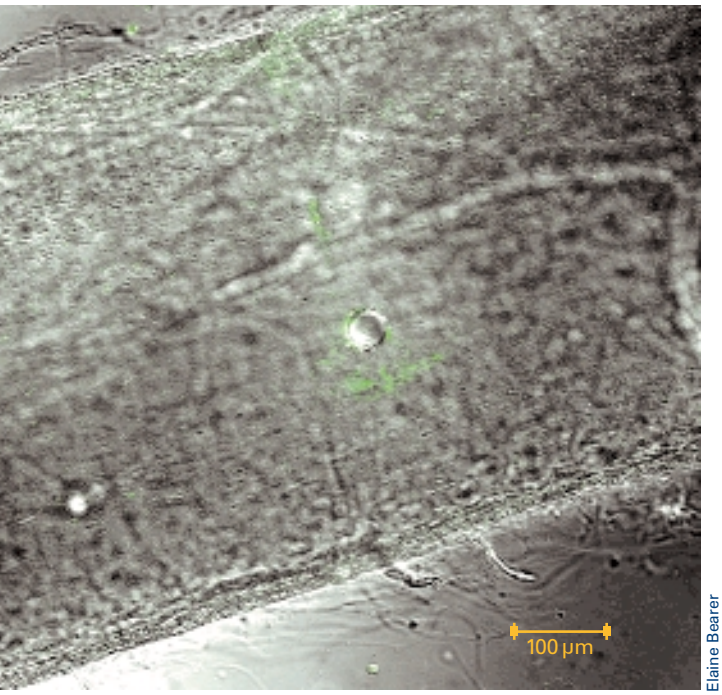


The NIGMS structural genomics project, formally called the Protein Structure Initiative, is designed to group proteins into structural families based on their gene sequences. The participating scientists plan to solve the structures of representative proteins from each family. These structures will provide valuable information about the relationship between gene sequences and protein structures. With this knowledge as a guide, scientists will use computer modeling to predict the structures of all other proteins, saving them the time-consuming work of solving these structures by traditional means.

For more information about the structural genomics initiative, see http://www.nigms.nih.gov/funding/psi.html.

Cell Movement Studies Track Herpes to its Hideout

Many NIGMS-supported scientists focus on individual cells—the fundamental units of life. By studying what happens inside, on, or around cells, researchers can reveal life's most basic and essential activities—how cells move, divide, or communicate with each other.



Elaine Bearer

◆ Bearer's team injected herpes virus particles into giant squid nerve cells to study how viruses travel inside cells. The virus appears green because it is labeled with a fluorescent protein. The round bead in the middle of the cell is an oil droplet that marks the injection site.

Take, for instance, the work of Elaine Bearer of Brown University and her colleagues. Their studies of how cells transport internal cargo revealed long-sought secrets about the herpes virus.

Herpes is a major cause of infectious corneal blindness as well as a host of other diseases ranging from cold sores to life-threatening brain inflammation. The disease is especially dangerous for infants and those with weakened immune systems.

Scientists already knew that even when a herpes infection seems to have receded, the virus hides out in nerve cell bodies, emerging periodically to cause new flare-ups. But until Bearer's group made it clear, researchers didn't know exactly how the virus travels from the nerve ending to the cell body.

The scientists track the virus as it travels in giant squid nerve cells. These cells are research favorites because they are enormous, making them easy to work with. Each cell is about 7 centimeters (2.75 inches) long and almost a millimeter wide—about the size of a small, straightened-out paper clip.

Bearer and her coworkers discovered that the virus moves in one direction, and it travels at the same constant speed as specialized cellular structures called organelles. The researchers concluded that the virus takes over the nerve cells' own internal transport machinery.

Other studies confirmed this, strongly suggesting that the herpes virus plays the same trick in humans. Understanding how the virus travels within nerve cells may lead to new treatments for herpes infections. It also teaches us more about cellular transport, a process that is essential to life.

Protein Fragments May Undergird New Cystic Fibrosis Drug

Cystic fibrosis (CF) is one of the most common fatal genetic diseases in the United States. Approximately 30,000 Americans have CF and an estimated 8 million are carriers of it.

John Tomich of Kansas State University and his colleagues designed protein fragments that may be the basis of a new drug to treat CF. These fragments, called peptides, may substitute for a protein that often malfunctions in those with the disease. This protein is called cystic fibrosis transmembrane conductance regulator, or CFTR.

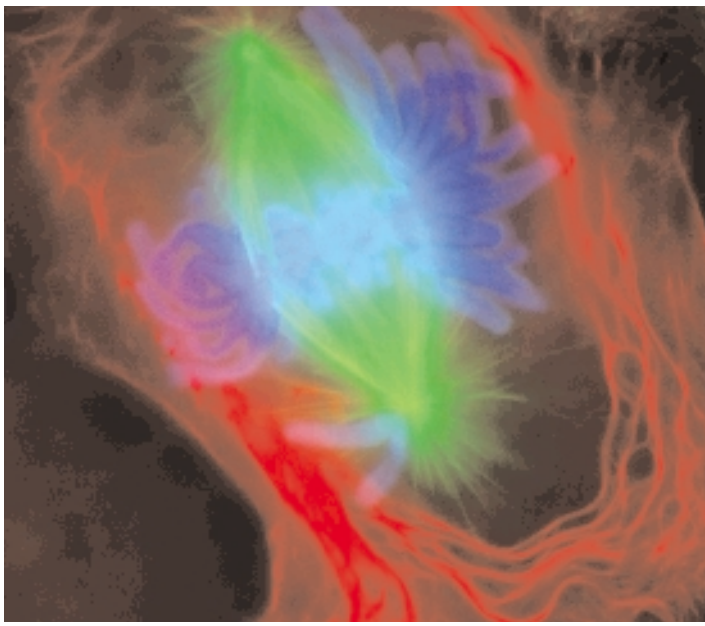
CFTR is an "ion channel protein" that controls the flow of chloride ions (a component of salt) into and out of cells. When CFTR does not work properly, the balance of salt inside cells is out of whack, leading to a build-up of abnormally thick mucus that clogs the lungs, intestines, and pancreas. Those with CF have trouble breathing and digesting food, and they frequently suffer from persistent lung infections.

Tomich's team discovered that bits of a brain protein similar in salt selectivity to CFTR can substitute for the defective CFTR proteins. These brain peptides form chloride channels that restore the salt balance in mice that have a genetic defect similar to the one in most people with CF.

If researchers can develop a peptide that forms chloride channels in those with cystic fibrosis, there's a chance it could help treat the disease. Toward that end, Tomich's group continues tweaking the brain peptides to improve their potential as drugs, such as their ability to be delivered and absorbed by cells. The scientists have already examined more than 100 variations of the peptides. Tomich is also interested in using the same strategy to treat other disorders, including stroke and epilepsy.

Studies of Dividing Cells Uncloak Cancer Cause

One of the most dramatic activities that cells accomplish is cell division, in which a cell must copy and sort out evenly all of its genetic material (chromosomes), then pinch itself in two. The complex dance performed by chromosomes just before cell division fascinates Conly Rieder, a cell biologist at The Wadsworth Center in Albany, New York. His team's work revealed how asbestos, previously used in ceiling tiles and insulation, can cause a wide variety of diseases, including lung cancer. By studying dividing newt lung cells, Rieder and his coworkers discovered that spearlike asbestos fibers can needle their way into the nucleus of a cell, where they may snag, sever, or stab chromosomes. In rare cases, the fibers may disturb chromosome sorting during cell division, which can lead to cancer and other disorders. Once asbestos fibers are lodged inside cells, they are passed on to each succeeding generation of cells, continually increasing the risk of serious genetic damage.



Conly Rieder

◆ Rieder's research team uses fluorescent dyes to label the dividing newt lung cells. The scientists use newt lung cells in their studies because these cells are large, easy to see into, and are biochemically similar to human lung cells.

Genetics and Developmental Biology

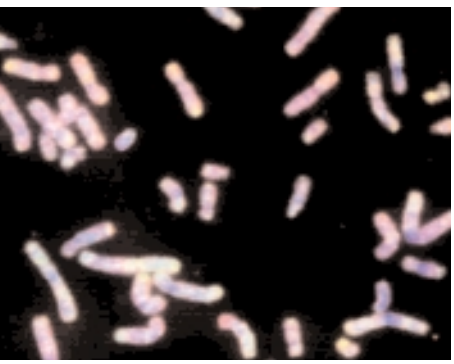
The Division supports research in:

- cell growth and differentiation
- control of gene expression
- developmental genetics
- chromosome organization and mechanics
- replication, recombination, mutagenesis, and repair of genes
- neurogenetics and the genetics of behavior
- population genetics, evolution, and the genetics of complex traits

A Focus on Heredity and Development

The Division of Genetics and Developmental Biology supports studies of how genes are inherited and how organisms develop from single cells. The eventual goal of these studies is to improve the diagnosis, treatment, cure, and prevention of human genetic and developmental disorders.

The Division also supports the Human Genetic Cell Repository (http://locus.umdnj.edu/nigms/). This cell bank houses an enormous collection of human cell cultures and DNA samples. The resource enables researchers to study the genetic basis of hundreds of diseases, including cystic fibrosis, Huntington's disease, a severe form of manic depression, and the eye disease retinitis pigmentosa.



Coriell Institute for Medical Research

The Cycle of Life

Just like a living creature, an individual cell has a life made up of stages. It is "born" (usually when its parent cell divides in two); it carries out its biological functions; it reproduces by dividing, often dozens of times; and it dies.

Underlying these milestones are regular cycles, which can last from less than an hour to years or even decades. Progress through each cycle is governed by a precisely choreographed biochemical cascade involving a repertoire of molecules with names like maturation promotion factor, cyclin, and cyclin-dependent kinase.

For the past several decades, NIGMS-supported researchers have conducted detailed studies of these molecules, methodically unraveling their biochemical identities and properties. The scientists have examined the molecules' ebb and flow throughout the cell cycle and their eventual demise as they are chemically chewed up when their job is done—until they are made again for the next cell cycle.

As for most life processes, when the biochemical choreography goes awry, the result can be disastrous. Glitches in the cell cycle can lead to a host of diseases, most notably cancer, which can be defined simply as uncontrolled cell division.

Scientists are poised to take advantage of the wealth of basic research on the cell cycle. They are testing scores of potential anticancer drugs that aim to bolster or block cell cycle molecules. Researchers are also harnessing their knowledge of the cyclical fluctuations in cell cycle molecules to predict the aggressiveness of a cancer and to tailor treatments.

Biology by the Clock

The cell cycle is by no means the only bit of biology controlled by the orchestrated fluctuation of many molecules. Another key example is the daily, or "circadian," rhythms of creatures as diverse as flowering plants, bread mold, fruit flies, and humans. The circadian rhythms of all

Woody Machalek

of these organisms rely on light, which activates an array of genes that control each organism's biological "master clock." These genes, many of them first identified in the fruit fly *Drosophila melanogaster*, are playfully given names like *timeless*, *clock*, *frequency*, and *double-time*.

In humans, the master clock regulates sleep-wake cycles, the release of various hormones, and a host of other biochemical activities. A better understanding of the inner workings of this clock promises to aid the treatment or prevention of sleep disorders, certain types of depression, and jet lag. The ability to manipulate the circadian rhythms of plants and animals could also have broad applications in the biotechnology and agricultural industries. Farmers could control when plants flower or go to seed, or they could breed drought-resistant plants by adjusting when leaf pores open and close.

Protecting Chromosome Tips

NIGMS-funded researchers are not only interested in what genes and chromosomes do, but also in what they look like and how they behave at various times throughout a cell's life cycle or an organism's lifetime.

At each end of every chromosome is a long chain of repeated DNA sequences called a telomere. Just as the plastic tips on shoelaces protect the laces from fraying, telomeres protect the ends of the chromosome from wearing away. Even so, telomeres in normal human cells become progressively shorter each time the cells divide. If the telomeres become too short, the cells either stop dividing and die, or they become vulnerable to genetic damage that can lead to cancer. This suggests that telomeres serve as molecular hourglasses that track how old a cell is and when it should die.

In some cells, an enzyme called telomerase helps maintain telomeres at a proper length by adding special DNA to the chromosome tips. Telomerase was first described by Elizabeth Blackburn, now at the University of California, San Francisco, and her former graduate student Carol Greider, now at The Johns Hopkins University. They discovered the enzyme in a single-celled creature called *Tetrahymena thermophila*, whose telomerase is always active.

In most adult human cells the enzyme is inactive, but it is turned on again in some cancer cells, allowing these cells to continue dividing even if they contain damaged DNA. Scientists are investigating whether shutting off telomerase in these cells could lead to new anticancer therapies.

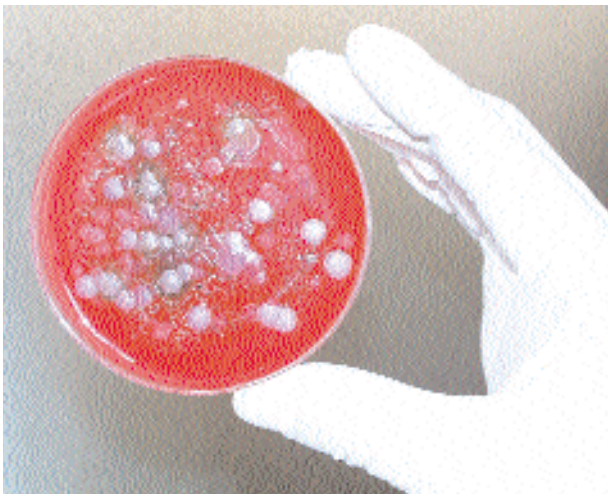
Fingerprinting Anthrax

Paul Keim, an evolutionary biologist at Northern Arizona University, studies how genomes evolve. He's investigated genetic variation in species ranging from microbes to endangered birds. But what he is now best known for is his group's technique to genetically fingerprint organisms that could be used as bioweapons, including those that cause plague, tuberculosis, and anthrax.

Keim and his coworkers study the evolutionary relationships among anthrax strains so they can trace a specific strain's lineage, even if it is subtly different from that of its ancestor. These studies aid investigations of bioterrorism by suggesting whether different attacks are carried out by the same person or group and revealing clues about the source of the bacteria.

The Keim technique was catapulted into prominence when it was harnessed by the FBI in the fall of 2001 to identify the strain of anthrax spores mailed in envelopes. The approach relies on slight genetic differences between the hundreds of known strains of anthrax. Keim's team detects these differences using a type of DNA fingerprinting technique related to that used in criminal and paternity cases.

The researchers also used this technique to analyze the strain of anthrax released in 1993 by the Japanese cult Aum Shinrikyo. Their study showed that the attack failed because the cult members used a veterinary vaccine strain of anthrax that is not dangerous to humans.



Paul Keim

◆ Anthrax colonies isolated from the 1993 Aum Shinrikyo bioterrorist attack in Kameido, Japan.

Like the work of many other NIGMS-supported scientists, Keim's research initially appeared to have little immediate medical significance. Now, it directly addresses a serious public health threat.

The Research Zoo: Bugs, Worms, Flies and More

Often, scientists conduct their research using cells from a variety of well-studied creatures, including a harmless strain of *E. coli* bacteria, yeast, a tiny worm nicknamed *C. elegans*, zebrafish like those found in aquariums, fruit flies, and mice. Using such "model organisms" allows scientists to control their experiments tightly and to build on existing knowledge about the organisms. Because the basic biology of model organisms is very similar to that of humans, these studies teach us, in molecular detail, how our bodies work.

Take the fruit fly. To most people, it is merely a tiny, annoying insect that buzzes around overripe bananas. To a geneticist, it is a window into human biology.

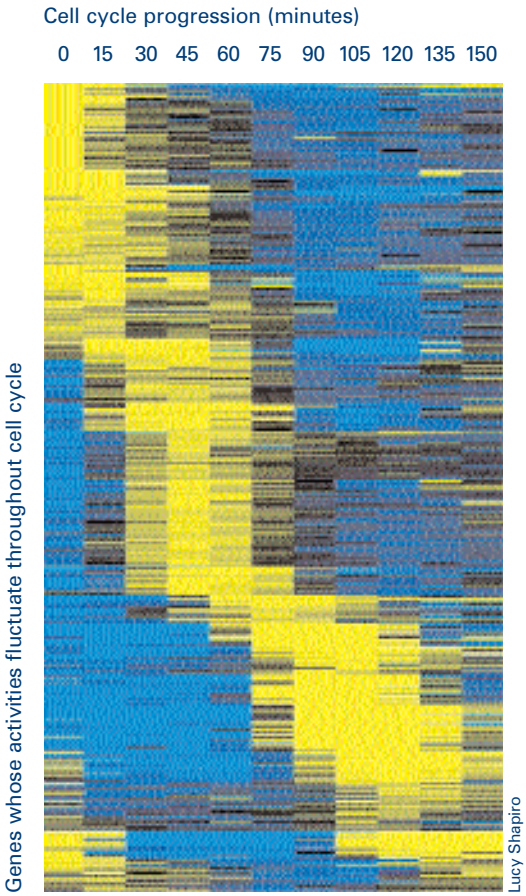
ZFIN

Microarrays Light Up Gene Activities

Now that scientists have at their fingertips the complete genetic sequences of a number of organisms, the next step is to figure out what all those genes do. One way to get this information is by using DNA microarray analysis. When a gene is "on," it lights up fluorescently on the microarray. This relatively new technology provides an instant visual read-out of the activity of thousands of genes—in some cases, an organism's entire genome.

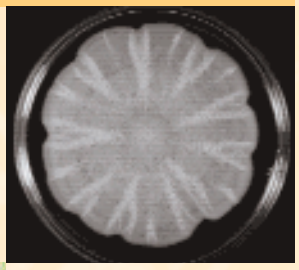
By using microarrays to learn which genes are expressed differently in normal tissues and in diseased tissues, researchers can diagnose a disease, reveal its molecular basis, or discover targets for drugs to treat it. Similarly, they can identify which genes change to transform a benign strain of bacteria into a deadly one.

Already, NIGMS grantees have used microarrays to analyze which genes in an organism are "turned on" at different developmental stages, in different tissues, or in response to drugs or other environmental factors. Lucy Shapiro of Stanford University, for example, uses microarrays to investigate which genes vary in their expression during the cell cycle. Her research team conducts its studies using the bacterium *Caulobacter crescentus*, which is harmless but is related to microbes that cause diseases in livestock and plants. This work may lead to new antibacterial drugs for use in medicine and agriculture.



◆ Using microarray technology, Shapiro's group discovered that the activity of 553 of the nearly 3,000 genes in the *Caulobacter crescentus* bacterium fluctuates throughout the cell cycle. The microarray read-out of these 553 genes is shown here, organized by when they are "on" (in yellow) and "off" (in blue).

Research on fruit flies, much of it supported by NIGMS, continues to reveal insights into areas of human genetics and behavior that range from genes that control the intricate branching patterns of blood vessels to the neurobiology of cocaine addiction.


Todd Reynolds, Whitehead Institute

Studies of model organisms reveal how malfunctions in cellular activities or components can cause disease. They also allow scientists to do preliminary tests of new therapies.


Bill Branson

Pharmacology, Physiology, and Biological Chemistry

The Division funds research in the following areas:

- bioorganic, synthetic, and medicinal chemistry
- bioinorganic chemistry and metal metabolism
- biochemistry, bioenergetics, and biotechnology
- glycoconjugates and glycobiology
- molecular immunobiology
- pharmacology and pharmacogenetics
- anesthesiology
- trauma and burn injury and wound healing

From Small Molecules to Whole Organisms

The Division of Pharmacology, Physiology, and Biological Chemistry supports research that ranges from basic chemistry to how the body responds to medications or traumatic injury. The goal is to understand life processes at a molecular level and to tease out the factors that make the difference between health and disease.

This Division also supports a training program called the Pharmacology Research Associate (PRAT) Program, which sponsors postdoctoral fellows who conduct research in the pharmacological sciences at NIH or Food and Drug Administration laboratories.

Personalized Medicines

Even if scientists are clever enough to develop and successfully deliver a drug that treats a certain disease, it just won't work for some people. For others, a normal dose could be fatal. The reason, in many cases, lies in our genes.

Genes are "recipes" for the body's workhorse molecules: proteins. When a medicine enters our body, it interacts with hundreds or thousands of proteins. Some of these proteins affect how well the medicine does its job. Tiny differences in these proteins, caused by each person's unique genetic make-up, govern how an individual will respond to a particular medicine. For instance, codeine is useless as a painkiller for a small percentage of people (the author of this booklet included) whose bodies cannot convert it into an active form.

To identify and catalog genes that affect our responses to medicines—a blossoming field called pharmacogenetics—NIGMS and other NIH components launched a coordinated, multimillion-dollar effort. Part of this initiative supports continued research, and part supports a database (http://pharmgkb.org) that catalogs the genes—and variations of these genes—involved in responses to medicines. This database will help scientists learn how common these variations are in the population and how they affect the

Combining Chemists to Fight Lupus

Sometimes, the spark of two minds working together can reveal surprising new ideas or discoveries. Such was the case for an unusual partnership between chemists working in very different areas who designed a potential new drug to treat lupus, a chronic inflammatory disease caused when a person's immune system attacks his or her own tissues. The potentially fatal disease is incurable, and medicines used to treat its symptoms often have severe side effects.

Gary Glick of the University of Michigan, Ann Arbor, and his group were studying antibody molecules that attack DNA, causing kidney damage similar to that seen in people with lupus. The research team of Jonathan Ellman of the University of California, Berkeley, was synthesizing a vast collection of different chemicals—and designing a fast, effective way to pick out the ones with a desired activity.

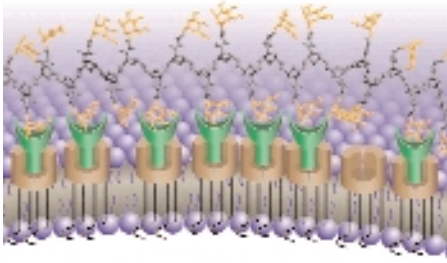
By rapidly screening through their library of compounds—created through an approach called combinational chemistry—the researchers found a molecule that prevents the disease in lupus-prone mice. The chemists are especially excited about the molecule because it appears to lack the serious side effects of current drugs. If the compound works as well in people, it may be the basis for a long-sought new medicine to treat lupus.

Sugar-Coated Cells and Inflammation

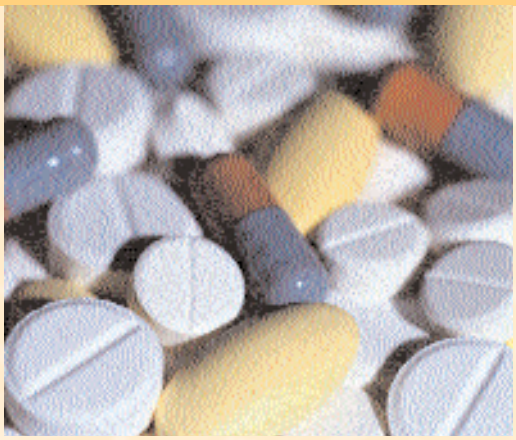
Most of our cells are studded with sticky, sugary molecules. These molecules allow cells to adhere to each other, which is key to activities that range from fertilization to infection. And they have captured the attention of chemist Laura Kiessling of the University of Wisconsin, Madison.

Kiessling focuses on sugar-coated molecules, called L-selectins, that guide immune cells to the site of an injury. The cells help fight infections, but when overzealous, they can cause inflammation.

Kiessling's group is able to control the behavior of L-selectin proteins—and entire immune cells—by baiting them with custom-made, super-sugary molecules. By acting as decoys that distract some of the immune cells, these molecules may minimize inflammation and may be the basis of new anti-inflammatory drugs.



◆ To study cell adhesion, Kiessling creates long, sticky carbohydrate molecules (orange and gray) that interact with receptors

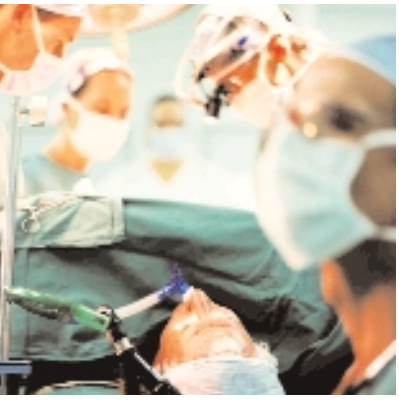


body's response to medicines. For details, see http://www.nigms.nih.gov/pharmacogenetics/. Some researchers have already transformed their pharmacogenetic studies into tests that may help physicians tailor treatments to individual patients and save lives. A team led by Richard Weinshilboum of the Mayo Clinic developed a test to predict how children will respond to a drug for leukemia. While the medicine effectively treats most with the disease, it can be fatal to children who have a tiny genetic variation in an enzyme that helps break down the medicine. In these children, the drug accumulates to toxic levels, literally poisoning them. Weinshilboum's group developed a simple blood test that they use to prescribe just the right amount of medicine to each child.

Investigating Anesthesia—and Alcohol

From the early days of ether and strong whiskey, anesthetics have been used for more than 100 years. But until recently scientists had only a fuzzy notion of how they work.

Traditionally, scientists thought anesthetics had no particular molecular target and deadened nerves merely by seeping into cells. A team of researchers led by Neil Harrison, now at the Weill Medical College of Cornell University, dislodged this notion. The group pinpointed the part of a specific molecule on the surface of nerve cells that is responsible for the action of two common inhaled anesthetics. Interestingly, the same molecular site also governs the intoxicating effects of alcohol.



This research may help scientists develop safer and more effective anesthetics. For instance, it may allow them to reverse the effect of these medications rapidly so that doctors can awaken patients immediately after surgery. It may also shed light on the molecular site responsible for alcohol's unpleasant effects—and perhaps on a new way to help treat alcoholics.

Saved by a Skin

Beauty, as they say, is more than skin deep. But for severe burn victims, that thin layer of skin stretches precariously between recovery and disability or death.

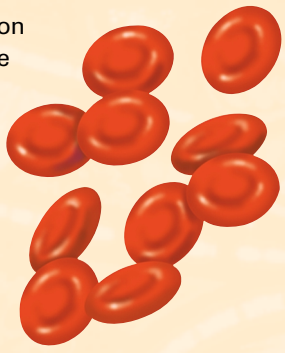
Our skin is not merely a convenient packaging to cover up our insides. It also protects our bodies from dangerous bacteria and viruses, regulates our internal temperature, and seals in our vital fluids. Patients with severe burns face their greatest risk from infection and from rapid, life-threatening fluid loss, which jolts the body into shock and massive organ failure.

NIGMS-funded scientists developed, and continue to improve upon, a type of artificial skin called Integra® Dermal Regeneration Template™, which is now the top-selling skin substitute in the world. Integra®, which looks somewhat like clear cellophane wrap, works as a temporary, protective covering that promotes healing. After removing the damaged skin, surgeons drape Integra® or a similar material over the wound and then apply a skin graft to encourage new skin growth.

Within 2 to 4 weeks, the patient's own skin cells grow into the scaffold provided by Integra®. Because patients with serious burns covering most of their bodies may not have enough healthy skin left to use for skin grafts, researchers are developing a way to grow sheets of tissue suitable for grafts from just a few of the patient's skin cells.

Improving Health for All: Confronting Disparities

Scientists have long known that some so-called "single gene" diseases are more common among certain populations: cystic fibrosis most often strikes Caucasians, sickle cell disease most often affects African Americans, and Tay-Sachs disease is most common among certain Jewish populations. There is strong evidence that genes associated with some of these diseases arose and concentrated in specific populations because they protected individuals from certain infectious diseases. For example, one copy of the sickle cell disease gene makes people more resistant to malaria. But those with two copies of the gene have sickle cell disease.



Normal Red Blood Cells

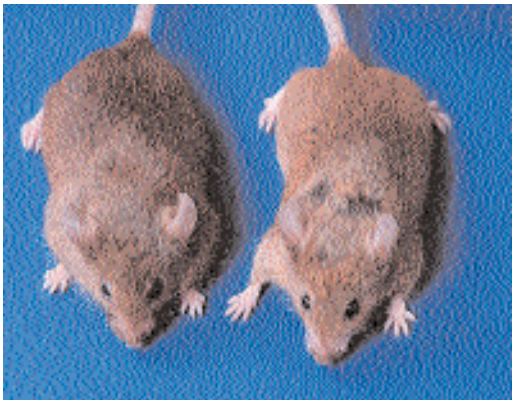
Many of the most common diseases probably involve several genes, as well as environmental factors. In many cases, the burden is greatest on minority and less affluent citizens, who have higher rates of cancer, birth defects, asthma, diabetes, and cardiovascular disease. Resolving health and disease disparities is one of NIH's highest priorities.

Thanks in large part to Integra® and to decades of basic, NIGMS-supported research on burns and wound healing, the grim prognosis faced by burn patients has brightened significantly. Twenty years ago, patients with severe burns over half their bodies rarely survived. Today, those patients usually recover—and so, incredibly, do some patients with severe burns over 90 percent of their bodies.

Designer Mice Eat More, Weigh Less

"Eat more, weigh less"—it sounds like the advertising slogan of a weight loss program. But it became reality recently for a certain type of genetically engineered mouse, providing tantalizing possibilities for treating obese humans. Obesity is responsible for the deaths of 280,000 adult Americans each year, making it a leading cause of preventable deaths in the United States. And it is an expensive one too—each year, the cost to treat problems caused by excess body weight reaches almost $100 billion.

Hope comes from the laboratory of Salih Wakil, a biochemist at Baylor College of Medicine. For more than 10 years, Wakil has studied an enzyme called acetyl-CoA carboxylase 2, or ACC2, that governs the body's ability to burn fat. His research group discovered that mice designed to lack this enzyme eat 20 to 30 percent more food, and yet have less body fat and weigh about 10 percent less than normal mice.



Salih Wakil

◆ When allowed to eat as much as they'd like, normal mice (left) tend to become overweight. Under the same conditions, mice lacking the ACC2 enzyme (right) actually eat more food but remain thinner.

Best of all, the engineered mice are otherwise normal, living long and breeding well. According to biochemical studies, the designer mice simply burn more fat than their normal counterparts.

If these results in mice hold true for humans, then a drug that blocks the function of ACC2 might allow people to lose weight while maintaining a normal diet. That, in turn, could reduce the incidence of diseases associated with excess body weight and obesity, such as diabetes, heart disease, stroke, and various cancers.

NIGMS is addressing the problem with a variety of approaches. Its pharmacogenetics initiative will likely reveal links between responses to medicines and genes that are more common in certain population groups. This knowledge could help doctors better identify and treat individuals who have these genes.

Sickled Red Blood Cells

NIGMS is also investigating how various population groups respond differently to traumatic injury. An increasing number of studies hint that there are underlying biochemical variations between men and women, as well as among racial and ethnic groups, that explain some of the different responses to injury and rates of wound healing. New information about these differences could improve doctors' ability to predict how trauma patients are likely to fare, especially which patients are at higher risk of developing a potentially fatal complication called systemic inflammatory response syndrome.

Bioinformatics and Computational Biology

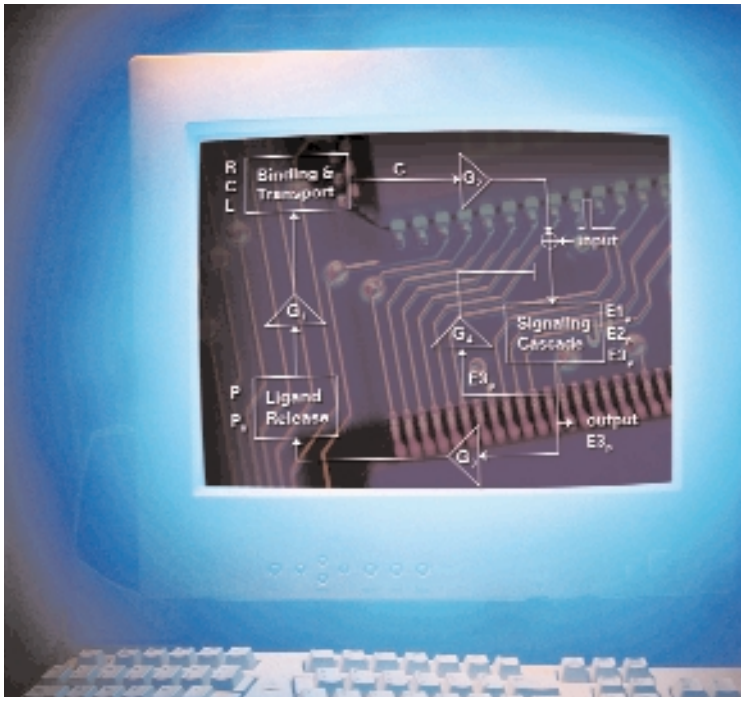
The Center supports the following areas:

- development and dissemination of databases, simulation programs, and other similar analytical tools
- theoretical and quantitative approaches to cellular, molecular, and developmental biology
- modeling studies of tissue- and organ-level homeostasis
- computational analyses of whole-body responses to medication or traumatic injury
- mathematical modeling of complex genetic traits

Bringing Computers Into Biology

The explosion of data from gene sequencing projects has left biologists scrambling to make sense of it all. Help comes from the field of bioinformatics, whose scientists organize and examine masses of data to reveal and extract new information.

Other scientists explore the vast, intertwined networks of factors that sculpt the behavior of whole cells, tissues, or organisms. These complex studies overwhelm traditional "reductionist" techniques that hammer out the roles of individual molecules. The solution is to use an entirely new method—computer modeling, which harnesses approaches from computer science, math, physics, and engineering.



Adapted with permission from *AJP–Cell Physiol*

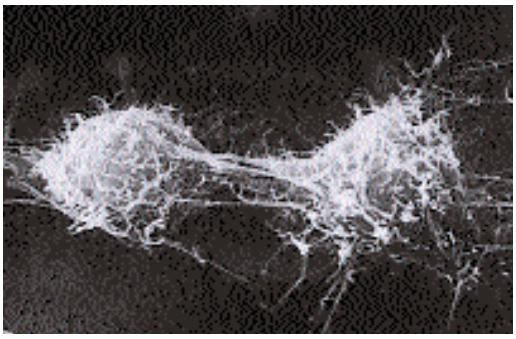
To support such computer-based strategies, NIGMS launched its newest component, the Center for Bioinformatics and Computational Biology (CBCB). This Center supports theoretical and quantitative studies of biological networks and dynamic processes.

Fields that already have a strong quantitative backbone—such as population biology, biophysics, biophysical chemistry, structural biology, and drug design—are supported within the NIGMS scientific divisions. The new Center focuses instead on recruiting investigators with mathematical and computational expertise to study processes like cell division, cell motility and mechanics, the assembly and dynamics of macromolecular complexes, signal transduction, metabolism, gene expression, and pattern formation in embryogenesis.

The Center supports multidisciplinary collaborations, sponsors workshops and meetings, defines the Institute's needs for database development and applications, and collaborates with other NIH components and Federal agencies in developing policies in this area.

Mining and Modeling Biology's Complexities

The research supported by CBCB focuses on a wide variety of systems, organisms, and biological processes. One example is work led by Douglas Lauffenburger of the Massachusetts Institute of Technology. His research team borrows an approach from electrical engineering to examine how a cell's behavior is governed by biochemical reactions on its surface. Using a signal processing circuit model, the scientists are able to explain, predict, and intentionally alter the behavior of cells.



Another researcher, Garrett Odell of the University of Washington, uses computer simulation to study the molecular gymnastics required for cells to move and change shape. His group focuses on protein molecules called actin and tubulin that assemble into long filaments, and myosin molecules, which chug like railcars along actin filaments.

The team's goal is to understand how all these molecules work together to mold cells into tissues in developing embryos. Because errors in early development underlie a variety of cancers and birth defects, understanding molecular details of the process may help treat or prevent these disorders.

Physicist Stanislas Leibler of Rockefeller University seeks to capture mathematically how myriad factors, including genes, interacting molecules, and environmental signals, weave together to control a cell's behavior. He and his collaborators focus on how bacteria respond to chemical changes in their environment—a process called bacterial chemotaxis that allows the bacteria to move toward food and away from noxious chemicals. Their models are designed to predict the bacteria's behavior under different conditions. To complement and refine this theoretical approach, they conduct laboratory experiments in which they alter the internal biochemistry of *E. coli* bacteria and examine how these changes affect the speed or accuracy of the bacteria's movement. Surprisingly, even genetically identical bacteria behave very differently. Leiber's group seeks to figure out why.

The researchers expect that their studies will reveal the connections between, and relative influence of, the network of factors that control bacterial chemotaxis. These "design principles" will in turn advance our understanding of many other biological signaling pathways.

Training Tomorrow's Scientists

So how do scientists develop the skills and get the experience to become leaders in their fields? In a word, training.

NIGMS trains more students to become scientists than any other component of NIH. The Institute has special programs to increase the number of physician-scientists and to encourage students from underrepresented minority groups to pursue biomedical research careers. For most of its training programs, NIGMS provides funds to universities and other institutions, which then select their own trainees.

The areas in which NIGMS supports training roughly mirror the fields in which it supports research. These include genetics, pharmacology, cell biology, biochemistry, computational biology, and biotechnology. A complete list of NIGMS training and fellowship programs is available at http://www.nigms.nih.gov/funding/trngmech.html.

Minority Opportunities in Research

This Division seeks to:

- increase the number and competitiveness of underrepresented minorities engaged in biomedical research
- strengthen the science curricula and biomedical research capabilities at minority-serving institutions
- build networks among individuals and educational institutions to promote minority participation in research
- enhance the research training opportunities for students and faculty at minority-serving institutions
- increase the flow of competitively trained minority students into graduate programs leading to the research doctorate

Addressing the Need for More Minority Scientists

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, the Division of Minority Opportunities in Research (MORE), seeks to enhance the science curricula and faculty research at institutions with substantial minority enrollments and to encourage minority students to train for scientific careers. Support is available at the undergraduate, graduate, postdoctoral, and faculty levels.

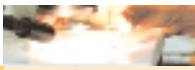
The underrepresented minorities targeted by MORE include African Americans, Hispanic Americans, Native Americans (including Alaska Natives), and natives of the U.S. Pacific Islands. For more information about the MORE Division and its programs, see http://www.nigms.nih.gov/about_nigms/more.html.

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.

Minority Biomedical Research Support Branch

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

The SCORE Program aims to assist the faculty at minority-serving institutions to develop competitive research programs. It supports faculty research projects that span the full range of topics supported by the various institutes of NIH. The RISE Program seeks to enhance the research environment at minority-serving institutions by funding activities such as attendance at scientific workshops and meetings, course development, and participation in research. The IMSD enables research-intensive universities to develop innovative programs that educate and train minority students in the biomedical sciences. At the time of this writing, nearly 700 faculty members, more than 1,000 undergraduates, and more than 750 graduate students at over 100 institutions were participating in MBRS research projects.



Insights from an MBRS Researcher

"I call it the G.I. Joe bug," says Leticia Márquez-Magaña, an MBRS researcher at San Francisco State University, referring to the bacterium she studies. When its food runs out, the normally sedentary bug, a common soil bacterium called *Bacillus subtilis*, goes into high gear. It squirts out bucketfuls of enzymes, zooms around in search of food, and employs all sorts of other biochemical survival strategies.

Finally, if things don't improve, the bug sporulates—the functional equivalent of transforming itself from a mushroom into a hibiscus. Márquez-Magaña teases out the genetic factors that orchestrate this dramatic transformation. Some of these factors allow disease-causing bacteria to resist the effects of antibiotic drugs, so understanding them in molecular detail may help scientists to design more powerful medications. Her studies will also shed light on the lives of harmful bacteria, such as *Pseudomonas aeruginosa*, which infects those with weakened immune systems, and *Salmonella typhimurium*, which can cause food poisoning.

Márquez-Magaña, who is co-director of the MBRS RISE program at her university, says the program has played two major roles in her career. First, it supports her research. This allows her both to continue the work she started while a graduate student at the University of California, Berkeley, and to launch a new study with a collaborator at Cornell University.

Jason Doiy

"I can let my scientific imagination run wild. And I have a whole team of people to help me indulge my creativity and test my hypotheses. How exciting is that?!" she exclaims.

Second, MBRS enables her to pursue one of her greatest passions—preparing students, particularly minorities, to become scientists. When she teaches graduate-level courses, Márquez-Magaña doesn't lecture from behind a podium. Instead, she uses a discovery-based approach to train students to think analytically, develop hypotheses, and design experiments to test those hypotheses.

She also teaches a class called "Strategies for Success in Grad School" that peels back the sometimes mysterious culture of science.

As a mentor, she finds her greatest fulfillment in helping others to excel. "I strive to empower students of color to reach their true potential," she says. "My ultimate goal is to empower them to become my colleagues."

Minority Access to Research Careers Branch

MARC supports special research training opportunities for students and faculty at 4-year, minority-serving institutions. The goal is to strengthen the training programs at these schools so they can prepare students for doctoral programs and careers in biomedical research.

MARC accomplishes these goals through Undergraduate Student Training in Academic Research (U*STAR) institutional grants, predoctoral fellowships, faculty fellowships, a visiting scientist program, and other training activities.

Currently, MARC supports nearly 650 undergraduates at over 60 institutions, 45 MARC predoctoral fellows, more than 70 predoctoral fellows in an NIH-wide program, and 2 faculty fellows.

Special Initiatives

MORE supports several special initiatives that strive to develop new approaches for the recruitment and retention of minority biomedical scientists. One such activity is the Bridges to the Future Program, which is co-sponsored by NIGMS and the NIH National Center on Minority Health and Health Disparities. This program assists 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). The Bridges Program currently supports over 1,000 students at more than 400 institutions.

The division also supports the MORE Faculty Development Award. This award enables faculty members at minority-serving institutions to update or enhance their research skills by working full-time for several months each year in a laboratory at a research-intensive university.

Another program, called the Institutional Research and Academic Career Development Award, provides postdoctoral researchers from research-intensive universities the opportunity to teach at minority-serving institutions. The goal is to motivate the next generation of minority scientists and to promote partnerships between research universities and minority-serving institutions.

NIGMS also collaborates with the Indian Health Service to link the Native American community with organizations that conduct health research. The program, called Native American Research Centers for Health (NARCH), encourages research on diseases relevant to American Indians and Alaska Natives, and seeks to develop a cadre of Native American scientists and health professionals who are able to compete successfully for NIH funding.

MARC: A Key to Success

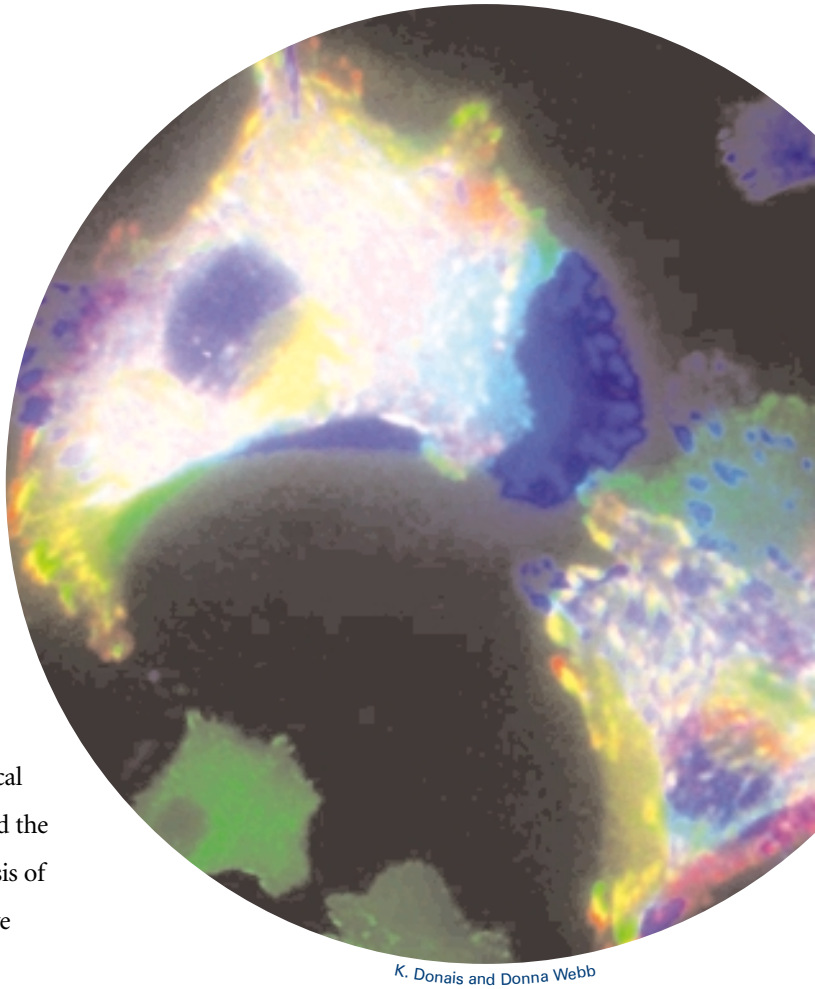
Identical twins Brian and Ryan Turner gained their first research experiences as MARC undergraduate students in the laboratory of Michael Summers at the University of Maryland, Baltimore County. The twins are now conducting research and studying medicine at Harvard University. They credit MARC with providing opportunities and training that are key to their current success. In Ryan's words:

Liza Green

As a MARC student, "I was exposed to many fields of research [including structural biology and virology] that increased my interest in science. During high school, I had no idea what research entailed. [In college, I learned that research] is fun and exciting…and [provides] the opportunity to think creatively and to test my own ideas."

For him, one of the most rewarding experiences of the program was attending conferences around the country to share his work and ideas with others in his field. "These research meetings are as much about the people as they are [about] the science," he says. "I recall many faces and names of people who became 'instant' friends. These are the people who I know will be the future of science."

Conclusion



K. Donais and Donna Webb

Science is a never-ending story. The solution of one mystery is the seed of many others. Research in one area may also provide answers to questions in other, seemingly unrelated areas.

The anticancer drug cisplatin unexpectedly grew out of studies on the effect of electrical fields on bacteria. Freeze-drying was developed originally by researchers as a way to concentrate and preserve biological samples. And a laboratory technique called the polymerase chain reaction became the basis of "DNA fingerprinting" techniques that have revolutionized criminal forensics.

Similarly, it is impossible to predict the eventual impact and applications of the basic biomedical research that NIGMS supports. But one thing is certain: These studies will continue to supply missing pieces in our understanding of human health and will lay the foundation for advances in disease prevention, diagnosis, and treatment.

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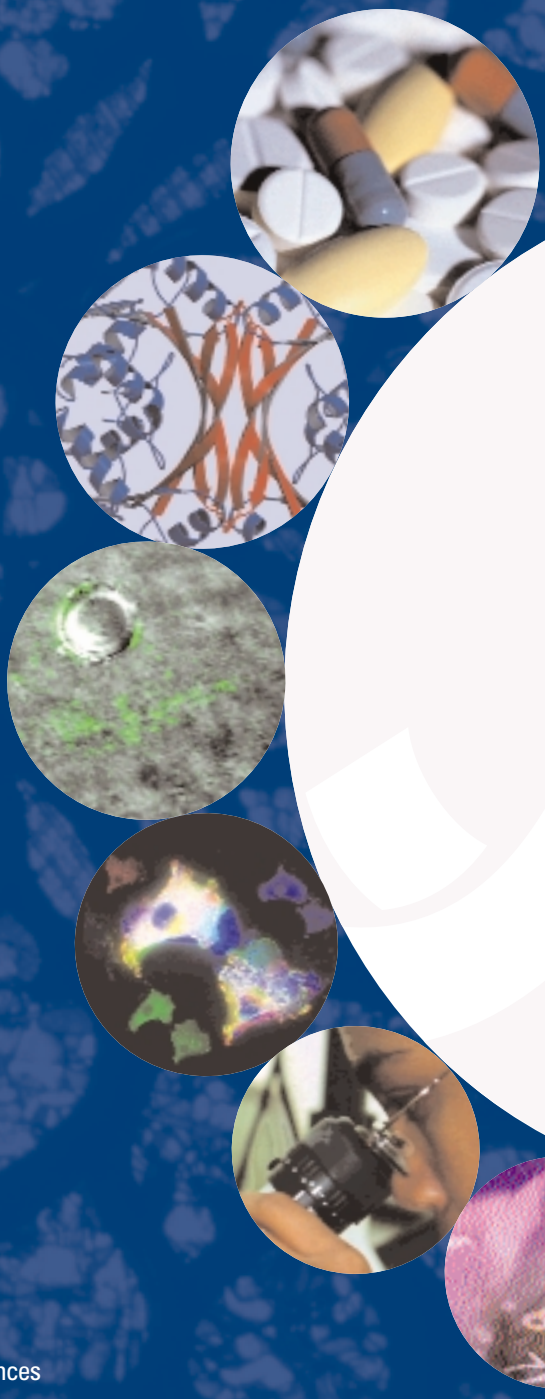

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