XVI.
National Institute of General Medical Sciences

INTRODUCTION

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training in the biomedical sciences. Although most of the research and research training are not disease oriented, NIGMS grantees contribute to the stores of new knowledge, theories, and ideas that form the foundation for the more disease-targeted investigations funded by other units of the National Institutes of Health (NIH). In addition, the NIGMS research training programs help to provide the most critical element required for outstanding research—well-prepared investigators with broad backgrounds in multidisciplinary research.

NIGMS began as the Division of General Medical Sciences in 1958 and became an Institute in 1962. In 1994, the Institute reorganized its research and training activities into four divisions. Three divisions award grants for research projects and research training—the Division of Cell Biology and Biophysics; the Division of Genetics and Developmental Biology; and the Division of Pharmacology, Physiology, and Biological Chemistry. Notable research projects of investigators in foreign countries receive support from these three Divisions of NIGMS. The Division of Minority Opportunities in Research funds research and research training grants to colleges and universities with high minority enrollments, through the Minority Access to Research Careers Branch and the Minority Biomedical Research Support Branch, respectively. This Division does not participate in the Institute's international activities.

Division of Cell Biology and Biophysics

The Division of Cell Biology and Biophysics focuses its resources on application of the research principles of basic physics and engineering sciences to biology. Its goal is to gain a greater understanding of the structural and functional relationships of cells, cellular constituents, and the constituent macromolecules that, in concert, form these cellular organelles. Studies supported by the Division consist of (a) basic research on the structure, function, and interaction of proteins and biopolymers and (b) investigation of the properties and functions of cellular elements. The ultimate goal is to prevent, treat, and cure diseases resulting from disturbed or abnormal cellular activity. The Division has two components: the Cell Biology Branch and the Biophysics Branch.

The Cell Biology Branch supports investigations related to the fundamental questions involving the function, structure, and regulation of cells, as well as the role of cellular dysfunction in disease. Problems addressed range from macromolecular assembly of cellular components to cellular motility and adhesion. The areas of study include the following:

- plasma and intracellular membranes, receptors, and signal transduction mechanisms;
- structure and function of the cytoskeleton;
- mechanisms of cell motility and cell division;
- regulation of protein and membrane synthesis and activation of cell growth;
- subcellular organelles and their role in cellular integrity; and
- biochemistry, cell biology, and biophysics of lipids, lipid synthesis, and lipid interactions.

The Biophysics Branch funds research in the areas of biophysics and bioengineering disciplines that use techniques derived from the physical sciences to examine the structure and properties of biological substances. This research includes the following:

- determination of the structure of proteins and nucleic acids;
- study of the structural features that determine macromolecular conformation;
- structural analysis of macromolecular interactions and ligand–macromolecular interactions;
- development of methods for and pilot studies of structural genomics;
- development of physical methods for analysis of molecular structures;
- development and use of theoretical methods to investigate biological systems; and
- fostering of bioengineering research on development and refinement of all forms of instruments and methods, bioanalytic techniques, and biomaterials needed to conduct research in the biological sciences.

Through National Research Service Awards (NRSAs), the Division maintains predoctoral institutional training grants and individual postdoctoral fellowships in biophysics, areas related to the chemistry–biology interface, and cellular and molecular biology. The Division also provides for research training of physician-scientists through the Medical Scientist Training Program, a combined medical and research doctoral (M.D./Ph.D.) training activity.

Division of Genetics and Developmental Biology

The Division of Genetics and Developmental Biology supports studies directed toward gaining a better understanding of the fundamental mechanisms of inheritance, development, and cell function. The findings of these studies contribute to the more targeted research projects supported by other NIH components. Most of the projects supported by the Division make use of nonhuman model systems. It is expected that the results of these investigations will lead to the eventual diagnosis, prevention, therapy, or cure of human genetic and developmental disorders. Among the areas under investigation are the following:

- regulation of gene expression;
- replication, repair, and recombination of DNA;
- RNA processing;

■ protein synthesis;
■ extrachromosomal inheritance;
■ population genetics and evolution;
■ developmental genetics;
■ cell-cycle control and cell growth and differentiation;
■ chromosomal organization and mechanics and rearrangement of genetic elements; and
■ neurogenetics.

The Division also supports NRSA predoctoral institutional training grants and individual postdoctoral fellowships, as well as one research resource, the Human Genetic Mutant Cell Repository.

Division of Pharmacology, Physiology, and Biological Chemistry

The Division of Pharmacology, Physiology, and Biological Chemistry supports a broad spectrum of research and research training aimed at improving understanding of fundamental biological processes at the molecular level and discovering approaches to their control. The Division supports research projects involving a multifaceted approach to problems in pharmacology, physiology, biochemistry, and biorelated chemistry that are basic in nature or that have implications for more than one disease area. The Division has two components: the Biochemistry and Biorelated Chemistry Branch and the Pharmacological and Physiological Sciences Branch.

The areas of research supported by the Biochemistry and Biorelated Chemistry Branch include the following:

■ enzyme catalysis and regulation and intermediary metabolism;
■ bioenergetics and redox biochemistry and glycoconjugate chemistry;
■ bioinorganic chemistry and electron transport and energy transduction;
■ organic synthesis and methods and medicinal chemistry;
■ synthesis of natural products, structure and function of small molecules, and development of new medicinal agents, including agents that mimic macromolecular functions;
■ drug discovery and design; and
■ biotechnology (biological catalysis and control processes).

The areas of study supported by the Pharmacological and Physiological Sciences Branch include the following:

■ drug actions and mechanisms of anesthesia;
■ new methods and targets for drug discovery;
■ interactions of drugs with endogenous mediators of physiological responses;
■ drug metabolism, drug-delivery strategies, and bioavailability;
■ regulation and pharmacological manipulation of receptors and channels, secondary and tertiary messenger systems, and mediator molecules;
■ pharmacogenetics;
■ total-body biochemical and physiological response to trauma and burns;
■ etiology of post-traumatic sepsis and the mechanisms of immunosuppression, wound healing, and hypermetabolism; and
■ molecular immunobiology.

The Division funds NRSA predoctoral institutional training grants in the pharmacological sciences and biotechnology, as well as the study of systems and integrative biology. This Division also funds postdoctoral institutional research training grants in clinical pharmacology and anesthesiology and in trauma and burn injury; individual postdoctoral fellowships; and the Pharmacology Research Associates Program, a postdoctoral fellowship program in the NIH intramural arena.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

First Structural Determination of a Yeast Mannosidase

A study at McGill University, Montreal, Quebec, is focusing on understanding the structure and function of two enzyme families—the class I α 1-2 mannosidases and α 1,2-mannosyltransferases. Assembly of *N*-linked glycoproteins, the most abundant class of cellular glycoproteins, requires the cotranslational transfer of oligosaccharide chains, synthesized on dolicholphosphate carrier molecules, to appropriate Asn-X-Ser/Thr sites of growing polypeptide chains in the lumen of the endoplasmic reticulum and Golgi apparatus of cells. Subsequently, these glycoproteins are processed in the Golgi apparatus. The extent of this processing is determined by the *N*-glycan α mannosidase family of enzymes. Appropriate oligosaccharide processing appears to be necessary for proper protein folding, as well as protein stability, biological activity, and cell-to-cell interactions, including bacterial, viral, and parasitic infection; cellular adhesion; and metastasis. The essential class I mannosidase enzymes are highly conserved from yeast to man, which makes them potential therapeutic targets for antimetastatic and antiviral agents. Similarly, the mannosyltransferase enzymes are found in yeast, where they are essential for cell wall biosynthesis and thus are targets for antifungal agents. Structures for these enzymes are therefore key to development of effective therapeutic agents. The researcher previously provided the first report of the crystallization of a glycosidase of *N*-glycan biosynthesis, and she has now solved the structure of this yeast mannosidase. This researcher presented her findings for yeast α 1-2 mannosidase at the meeting of the American Crystallographic Association, in Buffalo, New York, on May 22–27, 1999.

Crystallographic Studies of Ribosomal Particles

A scientist at the Weizmann Institute, Rehovot, Israel, has made important progress in elucidating, by x-ray crystallography, the structure of the small ribosomal subunit at the highest resolution yet achieved, 4.5 Å. This structure has revealed a number of key ribosomal features, including the site where protein biosynthesis is initiated, as well as clear views of the RNA molecules that are required for this fundamental cellular process. The investigator was able to obtain snapshots of protein biosynthesis in the "activated state" by triggering protein biosynthesis and by then flash freezing the crystals to -185°C. The high degree of resolution was achieved by preparing heavy atom derivatives of the ribosome subunit. The resultant image was constructed from twice the diffraction data collected elsewhere on this structure. The scientist's findings are the result of almost 20 years of pioneering research on the structure of the ribosome.

DNA–Protein Complex of *Bacillus subtilis* Bacteriophage

An investigator at Universidad Autonoma, Madrid, Spain, is studying the mechanism of protein-primed DNA replication in the bacteriophage phi29 of *Bacillus subtilis*. The long-term objective of this research is to find

specific ways to interfere with the initiation of viral DNA replication. Disease-producing viruses such as adenovirus and hepatitis B virus replicate by using similar protein-priming mechanisms.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Extramural Programs

Human Genetic Mutant Cell Repository

The NIGMS Human Genetic Mutant Cell Repository provides a valuable resource for investigators studying genetic disorders. It is located at the Coriell Institute for Medical Research, Camden, New Jersey. The repository collects, characterizes, maintains, and distributes cell lines from patients with a wide variety of genetic disorders and from healthy persons whose tissue serves as controls. Approximately 6,600 cell lines representing more than 350 diseases are available to qualified investigators. DNA samples from more than 1,300 of these cell lines are also available.

Cell lines in the repository are used for biochemical, cellular, and molecular studies to help elucidate the causes of genetic defects. In addition, the repository supplies DNA samples isolated from human–rodent somatic cell hybrids that are well characterized. Two complete panels are available for whole-genome mapping, and a growing number of chromosome-specific, somatic cell hybrid panels are also available. The hybrids are a valuable resource to investigators interested in determining the location of disease-related genes.

Also, the repository has acquired from Centre d'Etude du Polymorphisme Humain, Paris, France, approximately 800 cell lines from 60 families. The cell lines have been used for gene-mapping studies by a group of collaborating scientists around the world. The availability of these cell lines in the repository will greatly increase the access to this valuable resource and will also enable investigators, for the first time, to obtain the cell lines as well as DNA derived from them. Investigators working outside the United States purchase approximately 20% of the cell culture and DNA samples that are distributed each year.

Protein Data Bank

The Protein Data Bank is an international resource containing the three-dimensional coordinates of virtually all published macromolecular structures. It is accessible to researchers throughout the world via the Internet and through mirror sites in Europe and Israel. It is funded jointly by the National Science Foundation, NIGMS, the National Library of Medicine, and the U.S. Department of Energy. This database is an essential resource for scientists studying the structures of these macromolecules at atomic resolution and for the new protein structure initiative, which is designed to organize a cooperative, large-scale effort in the emerging field of structural genomics. Recently, the Protein Data Bank has begun collaboration with a new effort at the European Bioinformatics Institute, Cambridge, England. This new site will serve as the primary entry point of data from European scientists.

Foreign Research Grants

Principal investigators in appropriate research establishments in foreign countries are eligible to submit grant applications for research projects to the NIH. During fiscal year 1999, NIGMS funded 10 grants to principal investigators in three countries (Canada, Israel, and Spain) and supported four Postdoctoral Fellows from the United States in three countries (France, Germany, and the United Kingdom).

International Meetings

NIGMS joined other NIH Institutes in providing support for participation of U.S. and foreign scientists in the 9th International Conference on Biological Inorganic Chemistry, in Minneapolis, Minnesota, on July 11–16, 1999.