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 award grants for research projects and research training. 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 concerning 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 mechanisms;
- 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

Multidimensional NMR of HIV-Neutralizing Antibodies

The third hypervariable (V3) loop of the human immunodeficiency virus type 1 (HIV-1) glycoprotein 120 (gp120) is considered to be the principal neutralizing determinant of the virus and is involved in many aspects of viral infectivity. This loop was deleted from the constructs of gp120 studied by x-ray crystallography. With support from NIGMS, however, a scientist at the Weizmann Institute, Rehovot, Israel, used methods of solution and solid-state nuclear magnetic resonance (NMR) spectroscopy to determine the structure of this crucial loop bound to neutralizing antibodies. In fiscal year 2000 (FY 00), the 4th year of the project, these studies revealed that the loop has different conformations when bound to different antibodies, consistent with substantial flexibility in vivo. The face of the loop interacting with the chemokine coreceptor was identified. An unusual *cis*-proline detected in the loop is already serving as the basis for mimetics that inhibit infection of macrophages by human immunodeficiency virus (HIV) in cell culture, perhaps by disrupting the interaction of gp120 with the chemokine receptor.

Crystallographic Studies of Ribosomal Particles

A scientist at the Weizmann Institute, Rehovot, Israel, published two important reports on the structure of the small (30S) ribosomal subunit from *Thermus thermophilus,* as determined by high-resolution x-ray crystallography *(Proceedings of the National Academy of Sciences,* December 1999, and *Cell,* September 2000). In the 14th year of the project, FY 00, the scientist worked with scientists in three other research groups to attain the remarkable achievement of elucidating the structure of the ribosome. The complete ribosome (70S) structure, which is the largest and most complex ever determined by x-ray crystallography, represents the culmination of more than four decades of persistent effort. Although a number of other scientists joined the effort more recently, the Israeli scientist paved the way with her groundbreaking early research on ribosomes, working out many of the methods that eventually led to solution of the structure in FY 00. She was the first to attempt to crystallize such a large structure and the first to obtain a workable diffraction pattern that could be used to determine the structure.

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 (NIH), 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. The Protein Data Bank collaborates with the European Bioinformatics Institute, Cambridge, England, 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 FY 00, NIGMS funded 10 grants to principal investigators in four countries (Argentina, Canada, Israel, and Spain) and supported four Postdoctoral Fellows from the United States in three countries (France, Germany, and the United Kingdom).

International Conferences, Seminars, Meetings, and Workshops

NIGMS provided support for the participation of U.S. and foreign scientists at the following conferences:

- meeting on Frontiers in Anesthesia–Allergy, Immunology, and Mechanism of Anesthetic Action, at Niagara-on-the-Lake, Ontario, on June 10–12, 2000;
- FASEB (Federation of American Societies for Experimental Biology) Conference on Molecular Biophysics of Cellular Membranes, at the Vermont Academy, in Saxton's River, Vermont, on July 15–20, 2000; and
- Gordon Conference on Macromolecular Organization and Cell Function, at Oxford University, England, on August 6–11, 2000.

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