The Scripps Research Institute

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The Scripps Research Institute (TSRI), the country's largest private, non-profit research organization, has always stood at the forefront of basic biomedical science. Headed by President Richard A. Lerner, M.D., in just three decades the Institute has become internationally recognized for its work in immunology, molecular and cellular biology, chemistry, neurosciences, autoimmune diseases, cardiovascular diseases and synthetic vaccine development. Particularly significant is the study of the basic structure and design of biological molecules; in this arena TSRI is among a handful of the world's leading centers.

HISTORY

While its roots go back to the founding of the Scripps Metabolic Clinic in 1924 by philanthropist Ellen Browning Scripps, TSRI's modern beginnings date to the 1955 establishment of Scripps Clinic and Research Foundation, when a major portion of the Clinic's limited reserves were committed to the construction of a new research facility and to the recruitment of exceptional biomedical scientists.

In 1961, the institution recruited pioneering immunologist Frank Dixon and four of his colleagues from the University of Pittsburgh, researchers who were then contributing insightful observations on the causes and progression of autoimmune disease, to establish a Department of Experimental Pathology in La Jolla. Their work attracted others and the research program flourished and diversified into biochemistry, microbiology, virology, studies of blood coagulation, and cancer research. From the outset, the guiding philosophy of the research focused on clinical and basic investigations of the pathogenesis of human disease.

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In 1977 the multiple research programs that had developed were formally drawn together into the Research Institute of Scripps Clinic and by the mid-1980s laboratory space had grown to some 300,000 square feet. Major programs in cell and molecular biology, synthetic and bioorganic chemistry, and the neurosciences had developed, in addition to efforts in immunology and clinically oriented investigations.

As the faculty roster has grown, so naturally have the focus and number of areas of research. Today, TSRI scientists are actively investigating biological and chemical aspects of more than 40 diseases, including AIDS, alcoholism, allergy, Alzheimer's disease, cancer, cardiovascular disease, dementia, depression, diabetes, genetic diseases, hepatitis, infectious diseases, multiple sclerosis, renal disease, scleroderma, Sjogren's syndrome, sleep disorders, and diseases involving neural and muscular degeneration. Among other areas of research that cross specific disease lines are those that involve numerous investigations into the structure and function of proteins; biocatalysis and protein design; the factors, processes, and regulation of inflammation; bioorganic chemistry and molecular design; natural product synthesis; prebiotic chemistry; and the form and function of animal and plant cells.

In 1991, when Scripps Clinic and Research Foundation and Scripps Memorial Hospitals reaffiliated, the Institute became a separate corporation under the parent organization, Scripps Institutions of Medicine and Science. With that change its name became The Scripps Research Institute.

PHILOSOPHY

TSRI's philosophy emphasizes the compilation of basic knowledge in the biosciences for the application of medical discoveries; the pursuit of fundamental scientific advances through interdisciplinary programs and collaborations; and the education and training of researchers preparing to meet the scientific challenges of the next century.

FIG. 1. The Scripps Research Institute

The bulk of the Institute's funding is from the National Institutes of Health and other Federal agencies. In addition, collaborative industrial partnerships with leading pharmaceutical companies provide additional funding in several areas key to the organization's research objectives. Private philanthropy also continues to be an important source of funding for the Institute.

Currently housed in multiple laboratory buildings with more than 700,000 square feet of space overlooking the Pacific, the Institute's staff includes more than 230 principal scientific investigators, 600 postdoctoral fellows and more than 1,500 laboratory, administrative, and support services personnel. In addition, more than 100 students enrolled in TSRI's graduate program are working toward their doctoral degrees.

Rather than isolating faculty members and laboratories into separate and distinct disciplines, the generally prescribed university model, the cooperative, collaborative spirit is encouraged and embraced. Technicians, postdoctoral fellows, and administrative support staff all are given the latitude and responsibility to accomplish their tasks so as to serve the best interests of science.

MAJOR SCIENTIFIC ACHIEVEMENTS

- Developed and successfully tested the anti-leukemia drug 2-Chlorodeoxyadenosine (2-CdA, trade name: Leustatin).
- Demonstrated that rheumatoid factor is a product of an antibody gene that has maintained its "germlike" arrangement, explaining why so many rheumatoid factors are so similar.
- Developed a new and efficient method to produce monoclonal antibodies.
- Determined the complete, three-dimensional, atomic structure of the poliovirus.
- Pioneered the concept that small, synthetic peptides could replace larger peptide chains of bacteria and viruses for the purpose of making vaccines.
- Cloned the gene for the enzyme that is deficient in people with Gaucher's disease and developed a method to predict the severity of the disease.
- Purified the antihemophilic Factor VIII, a coagulation protein lacking in people with hemophilia A. Monoclate, the purified concentrate of Factor VIII, enables hemophiliacs to receive blood plasma that is free of contamination with viruses from blood donors.
- Synthesized surfactant, a lung material that keeps air sacs open and prevents respiratory distress syndrome.
- Pioneered the development of catalytic antibodies, opening new possibilities for protein synthesis and the rational design of new drugs.
- Mapped the prohormone for somatostatin in the brain and associated it with the primary neuropathic signs of Alzheimer's disease.

- Discovered a cell receptor for allergy-inducing IgE antibodies on lymphocytes, a finding that redirected research on the control of allergic diseases.
- Designed and synthesized a new class of molecules, known as enediynes, that represent some of the most potent anti-cancer agents ever tested and demonstrate unusual selectivity in their ability to destroy cancer cells while leaving healthy cells intact.
- Solved the three-dimensional structure of the enzyme superoxide dismutase (SOD), thereby establishing a direct link between mutations in the gene for SOD that lead to an unstable, less active enzyme and can cause amyotrophic lateral sclerosis (Lou Gehrig's disease).
- Completed the total chemical synthesis of the anti-cancer drug, Taxol, approved by the Food and Drug Administration for the treatment of ovarian cancer.
- Developed novel approach to inducing tumor regression by turning off neovascularization of the tumor, thereby setting the stage for the development of a new type of angiogenesis inhibitor.
- Determined the three-dimensional structure of the T-cell receptor, as well as its orientation bound to a major histocompatibility complex (MHC) molecule.

SCIENTIFIC DEPARTMENTS

The Skaggs Institute for Chemical Biology

The Skaggs Institute for Chemical Biology (Julius Rebek, Jr., Ph.D., Director) recently has completed its first full year of operation. Established by an extraordinary commitment from Aline and L.S. Skaggs, the Institute consists of more than 25 principal investigators with dual appointments in five departments, including Chemistry, Molecular Biology, Cell Biology, Neurobiology and Molecular and Experimental Medicine. The researchers have broad expertise in the structure of biological macromolecules, chemical and antibody catalysis, synthetic and combinatorial chemistry, molecular recognition, and molecular modeling methods.

A hallmark of the new Institute is the synergy that is encouraged between research groups. Four groups now work in molecular evolution, in areas that relate to the origins of life. The depth of this effort has made The Skaggs Institute the leading edge for research in the field. An initiative in RNA chemistry and biology is emerging; the intent is to develop structural and functional understanding of these key molecules of life that can ultimately lead to new therapeutic agents. In addition, cohesive efforts in drug design bring the Institute's structural and computational facilities for proteins and nucleic acids together with the expertise in organic synthesis and combinatorial chemistry.

Opportunities in newly emerging fields that blend chemistry with biology currently are being explored. These include biomaterial science, as well as the opportunities created by the sequencing of the human genome with the enormous array of small molecules being made through combinatorial chemistry. These disciplines will meet at the appropriate therapeutic target—the proteins, receptors, or nucleic acids associated with a particular disease.

Cell Biology

Because of the importance of cell biology in elucidating the basic mechanisms of health and disease, the Department of Cell Biology (Norton B. Gilula, Ph.D., Chairman) was established as an extension of TSRI's unique strength in integrating cell and molecular biology with molecular structure and chemical determinations. The department's efforts are focused in a number of areas related to the broad range of cellular functions and processes, including cell–cell communications; membrane receptor binding and signaling; the initiation and regulation of the cell cycle and mitosis; receptor-mediated endocytosis; intracellular trafficking; the structure and function of the nuclear envelope; genetics and genome analysis; the structure and function of the cytoskeleton; extracellular matrix–cell surface interactions; and growth factor regulatory mechanisms.

Scientists in the Division of Plant Biology within the department are utilizing the molecular biological techniques that have been developed in studies of animal systems and applying them to the biology of plants. Studies in progress range from basic investigations, such as the genetic control of photosynthesis and the structure and function of plant cell membranes and transport mechanisms, to more applied research including the use of plants to produce abundant quantities of antibodies and other mammalian proteins, and viral pathogenesis.

Chemistry

The mission of the Department of Chemistry (K.C. Nicolaou, Ph.D., Chairman) is threefold: to generate basic knowledge in the chemical and biological sciences on which applications to medicine, new materials and related areas may be founded; to connect fundamental discoveries through interdisciplinary programs and collaborations to biomedical and related applications; and to educate and train scientists in the chemical and biological sciences.

The department offers a broad scope of activities that blends sophisticated synthetic chemistry, molecular design and biocatalysis, and bioorganic chemistry. Organic synthesis is pursued as an advancing science. Both discovery and invention of new reactions and target-oriented total synthesis are investigated. In the area of new synthetic technology, research focuses on asymmetric catalysis, new catalyst design, bond-forming reactions and novel ring constructions. In total synthesis, complex biologically active natural products and other challenging molecules are targeted for synthesis.

The power of synthetic organic chemistry combined with chemical principles is utilized in molecular design, chemical synthesis and biological investigations of molecules with specific biological actions such as enzyme inhibitors, nucleic acid-cleaving molecules, and anti-tumor agents, as well as powerful chemical catalysts. Biological concepts and tools are used to design and produce large molecules such as enzymes and catalytic antibodies, and exploit their value in mechanistic and molecular recognition studies. Another primary area of focus is the understanding, improvement, and mimicking of enzymes. These efforts combine chemistry with the cutting edge tools of molecular biology, genetics, and immunology.

Immunology

Beginning in the 1960s, research in the Department of Immunology (Richard Ulevitch, Ph.D., Chairman) was focused primarily on the underlying biology of autoimmune and immunologic diseases. These initial studies developed a conceptual framework to explain how normal but inappropriate immune reactions can give rise to both local and systemic diseases.

During the past decade, the department has broadened its research base to include studies of the molecular basis of the immune response, including virus-induced immunodeficiencies, and the role of the cells of the vascular and inflammatory systems in human disease. Basic studies of the immune system include the genetics of the antibody response; T-cell immunity, including antigen presentation, thymic selection, and receptor signaling; tolerance induction and autoimmunity; and the stimulation, control, and biochemistry of inflammation.

Techniques that have been developed to isolate and screen virtually the entire antibody repertoire of humans or other mammals are being used to produce and recover scientifically and therapeutically useful antibodies that have potential against viruses and the mechanisms of autoimmune disease. Research in vascular biology and inflammation has led to a new understanding of the role of adhesion proteins in regulating tumor cell growth, the vascularization of tissues in diseases such as cancer, and the molecular mechanisms of blood coagulation.

Molecular Biology

The Department of Molecular Biology (Peter Wright, Ph.D., Chairman) takes an interdisciplinary approach to the study of the structure and function underlying normal and abnormal cellular processes. TSRI researchers are making contributions in the field through collaborative studies involving molecular genetics, molecular biology, protein engineering, and structural biology.

TSRI is one of the world's largest centers for structural biology and has achieved a number of scientific "firsts" in this area, including the first three-dimensional structure determination for a protein involved in cell-cycle regulation, the structure of the poliovirus, the structure of the T-cell receptor, and the structure for SOD.

Another major effort is in the area of computational molecular biology. Advances include improved methods and new computational approaches that are of fundamental importance for structure-based drug design. Further advances, using theoretical and experimental methods, have been made in the prediction of protein-folding pathways.

In the area of molecular engineering, important progress is being made on several fronts. New technology has been developed for the synthesis of artificial antibodies. Through a test-tube evolution process developed at TSRI, new ribozymes and antibodies with unique binding and catalytic activities have been created.

One of the department's main goals is to un-

derstand biological signaling events at the molecular level. A detailed understanding of the processes at the molecular level that result in large changes in biological systems is key to the design of novel agents that can be used to control disease.

Molecular and Experimental Medicine

The majority of studies in this department (Ernest Beutler, M.D., Chairman) seek to understand the life processes that, when disturbed, lead to disease. Thus, the research conducted is wide-ranging and involves several related fields of study, including blood coagulation, the biology of platelets, hemodynamics and bleeding disorders, and the role of thrombosis in cardiovascular and cerebrovascular diseases. The department also includes a clinical research component in the areas of the biochemistry of anti-cancer drugs, diabetes, and inflammation.

A pointed example of the clinical benefits that have resulted from work performed in the department is the development of Leustatin, an effective anti-leukemia agent and, in most cases, a drug that provides a cure for hairy cell leukemia. The drug was originally conceived as an agent that could provide a laboratory model for a type of immunodeficiency. As the work progressed it became apparent that it might have anti-cancer qualities. Animal studies were undertaken and subsequently, human trials were initiated at Scripps. A one-week course of treatment results in a cure for more than 80 percent of patients with none of the side effects associated with anti-cancer drugs. Further studies by Ernest Beutler, M.D. indicate that the drug may be effective against a number of immune disorders, including multiple sclerosis.

Neurobiology

The major scientific focus of the Department of Neurobiology (Gerald M. Edelman, M.D., Ph.D., Chairman) is on vertebrate development, in particular, the development of the nervous system. An emphasis is placed on how the brain develops its "wiring" and function to guide motion, perception, and sensation.

The fundamental question of development asks how the one-dimensional genetic code specifies the cellular events that result in a three-dimensional animal of a given species. The availability of modern cellular and molecular biology tools in recent decades has given rise to a view of embryonic development that centers on the cell and the gene as fundamental units of development.

Researchers here are addressing this problem by focusing on the brain in the earliest stages of development. The role of specific adhesion molecules in regulating cell–cell interactions is being examined in an effort to link knowledge on genetic information to events that direct cell division, movement, and eventual death.

These efforts suggest a link between cell adhesion molecules (CAMs) that control cell-cell binding, and substrate adhesion molecules (SAMs) that affect cell migration and transformations of cell states. For normal development to occur, the expression of CAMs and SAMs is co-regulated by precise genetic signaling. TSRI researchers have extended the scope of this work and identified a promoter and transcription enhancer for the gene encoding L-CAM. It was then shown that the enhancer region contained sequences that were regulated by homeobox genes—DNA sequences that play an important role in embryonic development.

Members of the department also study theories of how the brain functions in perception, work of relevance in understanding memory loss, dyslexia, recovery from stroke, and learning disabilities.

Neuropharmacology

Research in this department (Floyd E. Bloom, M.D., Chairman) is focused on gaining a better understanding of infectious, environmental and inherited diseases of the brain, and developing molecules that can act to reverse the disease process or stimulate normal repair mechanisms. In an effort to understand the mechanisms that lead to disorders of the brain, investigators have focused their efforts on a select number of problems, including drug and alcohol addiction, Alzheimer's disease, multiple sclerosis, and AIDS dementia.

Underlying these highly specific studies of various forms of brain and behavioral dysfunction are interactive research efforts into cell-signaling molecules and the parallel endeavor into the nature of neuronal–immune system interactions. Another primary area of research involves the biology of the largely overlooked supportive, immune, and inflammatory cells in the brain. The decision to reach beyond neuron-to-neuron events is another factor that sets the department's research efforts apart from other groups.

These efforts are focused in two directions.

The first is to determine the way in which viruses find and target cells in the nervous system, disturbing function, and often leading to cell death. The second area seeks to understand the ways in which glial and immune cells in the brain can cause disease.

Vascular Biology

The goals of the Department of Vascular Biology (David J. Loskutoff, Ph.D., Chairman) are to define the basic molecular and cellular mechanisms that guarantee the proper expression, function, and interaction of proteins and cells of the vasculature. The department brings together a cohesive group of investigators with interests in cell adhesion mechanisms, thrombosis, hemostasis, thrombolysis, and other areas of vascular biology and medicine. Dominant research themes include structure, function, and regulation of the proteins of the coagulation and fibrinolytic system, as well as the surface receptors on platelets and endothelial cells.

Emphasis is placed on the development of a greater understanding of the molecular and cellular basis for the formation and dissolution of fibrin, the main constituent of blood cells. Studies by TSRI investigators into these areas already have begun to provide insights into the diseases of the vasculature, including arteriosclerosis, thrombosis, stroke, hypertension, and bleeding disorders.

General Clinical Research Center

The William H. Black General Clinical Research Center (Francis V. Chisari, M.D., Director) provides facilities, staff and instrumentation for the performance of investigator-initiated, peer-reviewed research with human subjects. The Center further provides an environment that promotes investigative collaborations between research scientists and clinicians at Scripps Clinic to facilitate the transfer of basic scientific knowledge to the clinical arena and evaluation methods of patient treatment.

Established in 1974 with a gift from the Black Family and financed by a $12 million grant from the NIH, it is the only one of the 75 similarly funded centers in the United States not affiliated with a university or medical school.

Scripps Reference Laboratory

The Scripps Reference Laboratory (SRI) (David J. Bylund, M.D., Director) is a fully accredited, California-licensed clinical laboratory that develops, markets and performs numerous unique, high technology, medical diagnostic tests. SRI applies advanced technology from TSRI to the development of clinical diagnostic tests—principally in the areas of immunology, coagulation/thrombosis, and molecular pathology—that are utilized by physicians from around the world to detect some of the serious and often rare disorders of their patients. It serves as a reference laboratory for SmithKline-Beecham Clinical Laboratories in the United States and for Special Reference Laboratory, Inc., in Japan.

The division of research and development at SRI is responsible for converting basic research discoveries into clinically useful and applicable assays with full validation that includes technical optimization, quality control, standardization, clinical relevance, and the capacity to expand assays to batch sizes that are economically feasible. Each year the laboratory continues to develop new assays with applications to clinical trials and diagnostics and remains at the forefront of modern diagnostic laboratories.

EDUCATION

Education has always been an integral component of TSRI's mission. Over the years the Institute's researchers have prepared thousands of postdoctoral fellows and trainees for successful scientific careers. Because most of the important problems in biology and chemistry today require an interdisciplinary approach to their solutions, in 1989 TSRI established a unique graduate program to help integrate the disciplines of cell and molecular biology, structure and chemistry.

The Graduate Program in Macromolecular and Cellular Structure and Chemistry is an innovative program unlike any other in the United States. A second doctoral program in chemistry was established in 1981 in an effort to draw upon the superior capabilities of the TSRI chemistry faculty. The program's interactive nature emphasizes the collaboration of organic and bioorganic chemistry and biology, as well as the connection of fundamental discoveries through interdisciplinary activities. These five-year programs provide an exceptional training opportunity for a select group of intellectually diverse students.