THE SCRIPPS RESEARCH INSTITUTE

The Scripps Research Institute
An Overview

The Scripps Research Institute is one of the largest, private, non-profit scientific research organizations in the world. It stands at the forefront of basic biomedical science, a vital segment of medical research that seeks to comprehend the most fundamental processes of life. In a little more than four decades, it has made many major contributions leading to the betterment of health and the human condition.

History
In 1961, a group of five young immunologists led by Frank Dixon moved from Pittsburgh, Pennsylvania to La Jolla, California to start the Department of Experimental Pathology at what was then called the Scripps Clinic and Research Foundation (SCRF). The SCRF had been formed a few years earlier from the Scripps Metabolic Clinic, which was established in 1924 with a gift from local philanthropist Ellen Browning Scripps.

In 1977, SCRF became the Research Institute of Scripps Clinic, and, in 1991, the Research Institute gave up its direct affiliation with Scripps Clinic to become an independent corporation: The Scripps Research Institute

Research
One of the great challenges of modern medicine is to understand how and why diseases occur—diseases and conditions like stroke, heart disease, Alzheimer's, depression, schizophrenia, HIV and AIDS, hepatitis, alcoholism and drug addiction, rare genetic diseases, diabetes, lupus and other autoimmune diseases, kidney dysfunction, and cancer.

The Institute's 288 principal investigators, 775 postdoctoral fellows, 230 graduate students, and more than 1,500 technical and administrative staff ask not only *how* and *why*, but *what* can be done to prevent, treat, or eliminate these illnesses.

Scripps researchers are organized into seven departments—immunology, molecular biology, cell biology, chemistry, neurobiology, neuropharmacology, and molecular and experimental medicine—but many of their research projects extend across groups, departments, and disciplines.

This interdisciplinary climate is fostered by TSRI's unique setting and campus design.

Several of the 12 laboratory buildings on campus and much of the more than one million square feet of laboratory space is centered around common areas and shared facilities—supercomputers, centralized x-ray crystallography and mass spectrometry laboratories; a specialized electron microscopy and optical spectroscopy facility; a centralized DNA-sequencing core; and a fluorescence-activated cell-sorting facility, and one of the most advanced nuclear magnetic resonance facilities in the world, centered around a 900 MHz spectrometer, which is one of a handful in the world.

Nobel Laureates
Three of the Institute's current faculty are Nobel laureates:

-Kurt Wüthrich, Ph.D., 2002 Nobel Prize in Chemistry, "for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution;"
-K. Barry Sharpless, Ph.D., 2001 Nobel Prize in Chemistry, "for his work on chirally catalyzed oxidation reactions;" and
-Gerald M. Edelman, M.D., Ph.D., 1972 Nobel Prize in Physiology or Medicine, "for [his] discoveries concerning the chemical structure of antibodies."

Significant Faculty Honors
Three members of the faculty, K.C. Nicolaou, Ph.D., K. Barry Sharpless, Ph.D., and Chi-Huey Wong, Ph.D., are on the world's "most cited authors" list. This honor is accorded to less than one percent of all publishing scientific researchers from universities and scientific institutions for the past two decades.

TSRI's faculty also includes:

- 15 fellows of the American Association for the Advancement of Science;
- 14 members of the National Academy of Sciences;
- 11 members of the American Academy of Arts & Sciences;
- 4 members of the National Institute of Medicine;
- 4 members of the American Philosophical Society;
- 3 recipients of the California Scientist of the Year Award; and
- 3 recipients of the Wolf Prize in Chemistry.

Governance and Management
Richard A. Lerner, M.D., winner of the Wolf Prize in Chemistry and named California Scientist of the Year in 1996, is president of the Institute. He is supported by an administrative staff that manages the Institute's resources, including its intellectual property. Scientific departments are each managed by their chairs, and each investigator manages his/her own laboratory.

A Board of Trustees, comprised of 32 individuals from business, science, law, medicine, government, finance, and philanthropy, meets frequently and reviews major decisions concerning the policies, operations, and direction of the Institute.

A Scientific Board of Governors, comprised of 13 distinguished scientists from several countries, including eight Nobel laureates, meets annually to discuss the Institute's overall research goals and advises the President and other faculty.

Sources of Funding
The bulk of the Institute's approximately $280 million operating budget comes from grants from the National Institutes of Health and other federal agencies (TSRI ranks #1 in NIH funding to independent research institutions), through collaborative partnerships with leading pharmaceutical companies such as Novartis, and through philanthropic support from leading foundations, health-related associations, and generous individuals. In addition, funding is derived from licensing technology to private industry.

Major Scientific Achievements

Researchers at TSRI have been responsible for a number of seminal studies into the basic biology of molecules and cells that are at the root of all life. During the past two decades, scientists at the institute:

- Developed and successfully tested the **anti-leukemia drug** 2-CdA (marketed under the name cladribine (Leustatin) by Ortho Biotech, Inc., an affiliate of Johnson&Johnson). An intravenous medication with remarkably few side effects, 2-CdA now cures or produces many years of freedom from hairy cell leukemia in almost all those receiving treatment.
- 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 method to produce disease-fighting proteins called monoclonal antibodies thousands of times more efficiently than previously possible, an advance that has had a profound **impact on pharmaceuticals and the treatment of disease**.
- Determined the complete, three-dimensional, atomic structure of the **poliovirus**.
- Pioneered the concept that small, synthetic peptides -- the building blocks of protein structures -- 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,** a potentially fatal inherited disorder, and developed a method to predict the severity of the disease.
- Purified Factor VIII, a coagulation protein lacking in people with **hemophilia** A. Use of the purified concentrate greatly reduces the risk to hemophiliacs of infection from blood-borne AIDS, hepatitis, and other viral infections.
- Synthesized surfactant, a lung material that keeps air sacs open and prevents **respiratory distress syndrome**, a major killer of premature babies and adults.
- Pioneered the development of catalytic antibodies -- antibodies designed to function as enzymes in catalyzing specified chemical reactions -- 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 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 and selective anti-cancer agents** ever tested.

- Solved the three-dimensional structure of the enzyme superoxide dismutase , thereby establishing a direct link between mutations in the gene for this enzyme and **amyotrophic lateral sclerosis (ALS), or 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**.
- Discovered that antibodies can destroy bacteria, playing a hitherto unknown role in **immune protection**. Furthermore, the team found that when antibodies do this, they appear to produce the reactive gas ozone.
- Solved an x-ray crystal structure that provides the first detailed look at a membrane transporter protein, a finding that could improve **cancer therapy** and treatment for infection with **antibiotic-resistant bacteria**.
- Discovered an antibody that clears **prion infections** in cell culture, which has implications for the treatment of mad cow disease and its human equivalent.
- Elucidated the structure of an antibody that effectively neutralizes human immunodeficiency virus (HIV), the virus that causes **AIDS**.
- Cloned a gene that regulates **circadian rhythms** in plants, providing an increased understanding of the processes that enable organisms to anticipate and adapt to daily variations in the environment.
- Traced **human aging** and its associated diseases and conditions to a gradual increase in cell division errors in tissues throughout the body.
- Discovered a new paradigm in viral immunology: in **hepatitis B** infections, the immune system can cure viral infections without destroying the infected cells.
- Determined the three-dimensional structure of the T-cell receptor (TCR), a key component of the **immune response**. Understanding the structure of the TCR and its function may enable scientists to enhance the effectiveness of the immune system through the development of new, highly targeted therapeutics.
- Discovered that a fragment of the human protein tryptophanyl-tRNA synthetase (TrpRS) inhibits abnormal angiogenesis, the leading cause of **vision loss** in the United States, and this discovery may lead to new therapies, as abnormal angiogenesis is the leading cause of vision loss in the United States.
- Identified and isolated a protein that mediates the body's ability to sense cold and menthol through the skin—the first cold-sensing molecule ever identified and a potential target for **pain-modulating drugs**. Also, identified and cloned the first-known gene that makes skin cells able to sense warm temperatures.
- Created a form of bacterium with a genetic code that uses 21 basic amino acid building blocks to synthesize proteins—instead of the 20 found in nature. In addition to its **theoretical importance**, the work may give scientists a **powerful new tool for research**.
- Developed methods that have made possible the synthesis of compounds, especially those related to carbohydrates, which have pointed the way to "**green" methodologies in large-scale chemistry**.
- Instrumental in the process of developing Humira, a promising **rheumatoid arthritis** drug launched in January 2003.

Centers Within The Scripps Research Institute

The Skaggs Institute for Chemical Biology was established in 1996 with a commitment of $100 million by Aline and Sam Skaggs through the Skaggs Institute for Research and through their family foundation, the ALSAM Foundation. The Skaggs Institute's mission is to improve human health with cures for diseases by supporting research at the interface of chemistry and biology. In its first six years, more than a dozen principal investigators were recruited from leading academic institutions around the world. More than a thousand research papers have now been published by scientists affiliated with The Skaggs Institute.

Institute for Childhood and Neglected Diseases (ICND) was created in 2001 to apply the new molecular understanding of biology to the challenge of reducing and treating childhood and neglected diseases, such as malaria, epilepsy, mental retardation, cystic fibrosis, chronic pain, and depression. Housed in a new, state-of-the-art 54,000-square-foot laboratory building on the east side of TSRI's campus, the ICND is an umbrella group within TSRI for young scientists who are working in areas relevant to the institute's focus on these sometimes widespread and often devastating diseases.

The Helen L. Dorris Institute for the Study of Neurological and Psychiatric Disorders of Children and Adolescents, founded in 2002 with a generous grant from mental health advocate Helen L. Dorris, aims to uncover the pathological basis of mental disorders and to enable the development of therapeutic approaches.

The Harold L. Dorris Neurological Research Center, established in 1999 as the result of a major gift and long-term commitment by the Harold L. Dorris Foundation under the direction of Helen L. Dorris**,** has attracted an international cadre of scientists from such disciplines as neurology, immunology, chemistry, molecular biology, and endocrinology to conduct research into neurological disorders.

The General Clinical Research Center (GCRC), established in 1974 with a generous gift from Mrs. William H. Black and Mr. and Mrs. William F. Black, and later supplemented by a donation from the Stein Endowment Fund, enables researchers to test the clinical utility of discoveries made in the TSRI's laboratories. Located in a wing of Scripps Green Hospital, the GCRC manages a seven-bed inpatient unit, and an adjacent outpatient suite. Studies at the center have tested the safety and efficacy of potential small-molecule drug treatments and have looked at the underlying mechanisms of illnesses such as thrombotic and cardiovascular diseases, alcoholism, infectious diseases, sleep disorders, allergic and autoimmune diseases, neurogenerative diseases, and cancer.

The Center for Integrative Molecular Biosciences (CIMBio) is a new, interdisciplinary facility organized to bring together the talents of several TSRI groups in divergent disciplines such as chemistry, biochemistry, structural biology, and cell biology. The investigators' interests converge in one area—the structures of the tiny machines that buzz with activity inside cells. Members of CIMBio seek to speedily unravel and analyze these structures through the combined use of x-ray crystallography and electron microscopy (EM). The centerpiece of CIMBio and the focal point for the building design is a microscopy suite containing six state-of-the-art electron microscope rooms.

Education Programs at The Scripps Research Institute

Ph.D. Graduate Education

Because most of the important topics in biology and chemistry today benefit from an interdisciplinary approach, the Macromolecular and Cellular Structure and Chemistry Graduate Program, leading to the award of a Ph.D., was established in 1989 to draw on the institute's expertise in disciplines such as cell and molecular biology, immunology, molecular medicine, neurobiology, and chemistry. In an effort to draw on the superior capabilities of the chemistry faculty, a Doctoral Program in Chemistry was established three years later. The 2002 *U.S. News & World Report* academic rankings listed the two programs at TSRI among the top 10 in their fields in the country. The publication also ranked TSRI second in the specialty of organic chemistry.

In 2002, TSRI named its graduate college the Kellogg School of Science and Technology to honor philanthropists Janet R. ("Jean") Kellogg and W. Keith Kellogg II, who have been long-standing patrons of education and science. In the 2003-2004 academic year, there were 222 graduate students in the Kellogg School of Science and Technology and 146 alumni with Ph.D.s.

The Skaggs Oxford Scholarship program is a joint five-year doctoral degree program in biology, chemistry, and biochemistry that trains young scientists at both TSRI and the University of Oxford. It is funded by TSRI in appreciation of the generosity of long-time supporters L.S. and Aline W. Skaggs.

Postdoctoral Fellows

In its 40-year history, TSRI has trained thousands of postdoctoral fellows from around the world. Currently there are more than 750 continuing their scientific training for a period of two to five years, contributing to ongoing research, and publishing their results in collaboration with and under the guidance of a principal investigator.

Educational Outreach to Local Teachers and Students

The institute provides opportunities for students and teachers from throughout San Diego County to participate in research activities on the campus. While students of all ethnic and cultural groups are accepted into the programs, a special emphasis is placed on identifying and recruiting students who are historically underrepresented in the sciences.

In the Summer Research Internship Program, teachers, high school students, and undergraduates work full-time for eight weeks conducting basic biomedical research in a laboratory under the supervision of a TSRI scientist. Two spring programs bring local teachers and high school students to the institute once a week for six to eight weeks for courses and hands-on experiments on state-of-the-art research topics and techniques. Two annual one-day symposia, "Contemporary Issues in Bioscience" and the "X-Sci" science fair, feature scientific presentations and interactive laboratory tours for local teachers and students, respectively.

Funding for TSRI's educational outreach programs comes from local private foundations, whichhave included the Samuel H. and Katherine W. French Fund and the Maurice J. Masserini Charitable Trust, both administered by Wells Fargo Bank; the San Diego Workforce Partnership, which funds 10 to 15 internships a year through the Neighborhood House Association; the Joseph Drown Foundation; the Carl E. Wynn Foundation; and the Bank of America Foundation. In addition, private contributions have been received from philanthropists Robert Wallace; George and Patsy Conrades; and Oliver and Norma James. Endowment funding for the outreach program includes gifts from former Chairman of the TSRI Board of Trustees John Diekman and his wife Susan Diekman; The William Randolph Hearst Foundation; and the Arthur Vining Davis Foundation.

For further information: www.scripps.edu