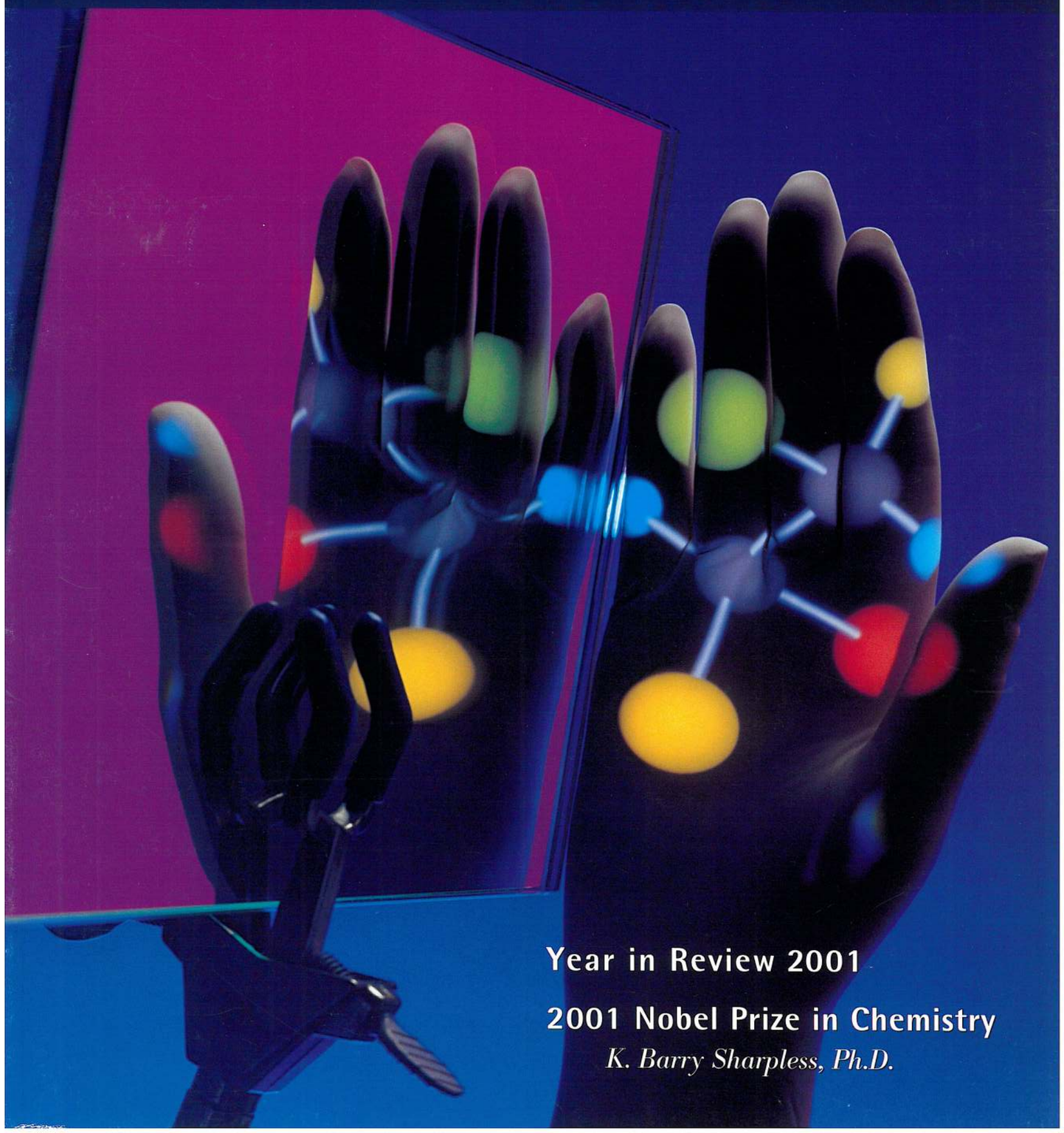
VOLUME FOUR | NUMBER TWO

The Scripps Research Institute

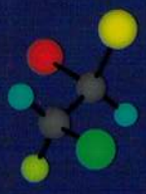
Endeavor



Year in Review 2001

2001 Nobel Prize in Chemistry

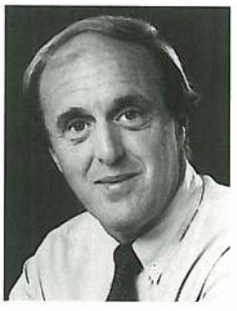
K. Barry Sharpless, Ph.D.



Most of the life molecules, such as amino acids, carbohydrates, and nucleic acids are chiral, or "one-handed," i.e. their mirror images are not superimposable, just like our hands. Although only a subtle difference, chirality often results in dramatically different biological properties. While nature makes molecules of a desired chirality with ease, their synthesis in the laboratory was very difficult, if not impossible, until recently. TSRI professor K. Barry Sharpless, Ph.D., who has been awarded the 2001 Nobel Prize in Chemistry (together with William S. Knowles and Ryoji Noyori), has pioneered methods for stereoselective oxidations of olefins, the most abundant starting materials produced by petrochemical industry from oil. Today, chemists around the world, in both academic and industrial settings, routinely use the Sharpless Asymmetric Epoxidation, Dihydroxylation, and Aminohydroxylation in drug discovery and manufacture. This work is a result of more than 20 years of research by K. Barry Sharpless, and co-workers.

year in review 2001

Endeavor



In a year punctuated by significant scientific achievements and the acquisition of substantial grant funding, the quintessential event in the collective life of The Scripps Research Institute was the awarding of the 2001 Nobel Prize in Chemistry to K. Barry Sharpless, W.M. Keck Professor of Chemistry and member of The Skaggs Institute for Chemical Biology. Coming so closely on the heels of the tragedy of September 11, this prodigious accomplishment lifted the spirits of the entire organization, as we came together in celebration of Barry's remarkable scientific career. Long recognized by the scientific community, his work has received considerable attention from the philanthropic community, most notably Sam and Aline Skaggs, whose contributions have enabled him to achieve numerous research breakthroughs. Sharpless was lauded by the Nobel Committee for his work on chirally catalyzed oxidation reactions. He has contributed innovations to the development of broadly useful and commercially practical catalytic oxidation chemistry for the selective production of bioactive chiral molecules with the proper right- or left-handedness.

Late this year, a dedication ceremony was held for the new Institute for Childhood and Neglected Diseases and the Helen L. Dorris Institute for the Study of Neurological and Psychiatric Disorders of Children and Adolescents, both housed in a laboratory facility on the east side of TSRI's campus. A lead gift from John and Becky Moores created the impetus for a successful fund-raising campaign for the Institute for Childhood and Neglected Diseases, which was spearheaded by Bernie and Marc Chase. This research initiative will apply the new molecular understanding of biology to address, reduce, and treat recalcitrant illnesses in two major categories: childhood diseases and neglected diseases that affect populations primarily in developing countries. Helen Dorris's particular interest in mental health advocacy led her to provide the funding to establish the institute that bears her name, with a strong emphasis on neurologic and psychiatric disorders. The institute will be headed by Benjamin Cravatt, Assistant Professor, Department of Cell Biology and The Skaggs Institute for Chemical Biology.

TSRI scientists have been selected to lead three multi-year consortia funded by the National Institutes of Health to study important questions in basic biology. A $35 million grant has been awarded to establish The Integrative Neuroscience Initiative on Alcoholism. Headed by George F. Koob, Professor, Department of Neuropharmacology, the program aims to combine physiologic, molecular, and cellular models to determine the genetic and environmental factors that form the basis for individual differences in the development of excessive drinking. The initiative will address the basic science of alcoholism and will establish a platform on which future treatments can be built.

James C. Paulson, Professor, Department of Molecular Biology, will lead a consortium of basic scientists dedicated to studying carbohydrate function. Made possible by a $34 million grant from the National Institutes of Health, the Consortium for Functional Glycomics will bring together a large group of scientists from leading academic medical centers across the United States to identify carbohydrate molecules that collectively play important roles in cell communications. Ultimately, scientists expect that many of the findings will enhance understanding of the immune system.

Ian Wilson, Professor, Department of Molecular Biology and The Skaggs Institute for Chemical Biology, spearheads the Joint Center for Structural Genomics, an initiative funded by the National Institutes of Health. The center draws on talent from several California institutions in addition to TSRI, including the Genomics Institute of the Novartis Research Foundation; University of

California, San Diego; and the Stanford Synchrontron Radiation Laboratory. The consortium has received a grant of $24 million for a 5-year period to expand on the body of knowledge made available by the completion of the human and other genome sequencing projects. Its goal is to determine the 3-dimensional structure of up to 2000 proteins by developing high-throughput technology, thereby advancing efforts to understand structure-function relationships important for diseases and treatment of diseases.

In June, the most powerful, high-resolution nuclear magnetic resonance (NMR) spectrometer, a 900-MHz machine, was delivered to TSRI. The new spectrometer became the centerpiece of one of the world's most prominent collections of NMR instruments; 10 instruments have a power of 500 MHz or greater. The new spectrometer, the first of its kind, was several years in the making by Bruker Instruments, Inc. NMR spectroscopy provides atomic coordinates of a wide range of biologically important molecules in solution. This information enables scientists to determine the structure-function relationships of molecules that lie at the heart of understanding fundamental biological processes.

As has become the norm at TSRI, scientists this year published more than 1000 articles in peer-reviewed scientific journals, bringing their knowledge and insights to bear in a significant way on the body of scientific knowledge. A collaboration between Ian A. Wilson, Chi-Huey Wong, and their colleagues in the Departments of Chemistry, Molecular Biology, and The Skaggs Institute for Chemical Biology yielded one of the best views ever of an enzyme caught in the act of catalyzing a reaction on the enzyme's substrate. This research should be valuable as a tool for drug synthesis, because it will enable scientists to engineer this enzyme to alter or improve its specificity.

In addition, researchers in Dr. Wilson's laboratory, in collaboration with colleagues at Oxford University, determined the structure of an antibody that effectively neutralizes HIV. This discovery may provide a basis for the design of effective vaccines against the virus. Normally, antibodies that the body produces to fight HIV are ineffective because much of the surface of the virus is inaccessible. In addition, antibodies mostly recognize long protein loops on the outside of the virus, and in the body HIV rapidly mutates so that the loops become unrecognizable. This neutralizing antibody, however, appears to be effective against a wide variety of HIV isolates. In addition, this antibody is the first human antibody whose entire structure is known.

Work in my laboratory this year led to the discovery that antibodies have a novel catalytic ability — unique among proteins — that could mean that they do more to protect our bodies than researchers had previously thought. My colleagues and I found that antibodies can catalyze the formation of hydrogen peroxide from singlet oxygen. Antibodies could have played a role as ancient proteins whose function was to remove singlet oxygen. In fact, before the antibody-mediated immune response evolved in vertebrates hundreds of millions of years ago, an ancient form of antibodies may have existed, molecules whose role was to catalyze singlet oxygen destruction. The work opens up possibilities for new therapies for conditions ranging from bacterial and viral infections to cancer. Further, the ability of antibodies to generate toxic compounds may be linked to a number of autoimmune diseases.

Appearing this year on the cover of *Science* magazine was Geoffrey Chang's elucidation of an x-ray crystal structure that provides the first detailed glimpse of a membrane transporter protein. This finding could be useful for improving cancer therapy and fighting antibiotic-resistant bacteria. One of the ways that bacteria resist antibiotic drugs is by using membrane transporters, large proteins that sit in the cell membrane and move other molecules in and out. In human cells, one of the

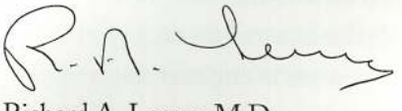
important roles of these transporters is removal of injurious toxins. Unfortunately, harmful bacteria use transporters to nullify antiobiotics; certain cancer cells do the same thing. Dr. Chang's structure is considered a breakthrough, opening the door for scientists to design a new class of drugs that patients would take in conjunction with antibiotics or chemotherapeutic agents to keep those medications in the cells and increase their efficacy.

Dennis Burton and Anthony Williamson designed an antibody that clears prion infection in cell culture. This finding may point the way to a treatment for mad cow disease and its human equivalent. Diseases such as mad cow disease are unusual because the infectious material is not a virus or a bacterium. Rather, the material is malformed prion protein, molecules that start out with one shape that is innocuous and end up with another form that is deadly. The newly engineered antibody seems to halt the infection completely, binding to the normal form of the protein and preventing the infectious form from binding in cell culture. Potentially, a drug might be designed to bind to the same place as the antibody in humans.

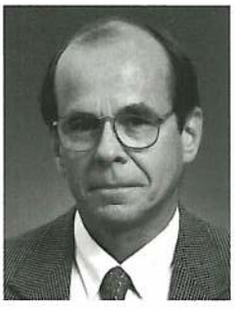
Scientists at The Skaggs Institute for Chemical Biology published two separate articles in which they described different ways of engineering bacterial cells to encode "unnatural" proteins. These proteins differ from those produced by other living organisms because the unnatural proteins incorporate novel amino acids. The methods could provide powerful mechanisms for studying protein and cellular functions, because the results establish that bacterial strains can be made to incorporate novel amino acids into proteins. Further, the results could enable scientists to envision the possibility of engineering completely new proteins. Peter Schultz and Paul Schimmel led the two separate efforts.

A number of our scientists were honored this year with prestigious awards, testimony to the value that the scientific community places on their research contributions. In addition to the Nobel Prize, Dr. Sharpless received the Wolf Prize in Chemistry and the Franklin Institute Award. Tamas Bartfai received the Ellison Medical Foundation Senior Scholar Award, and Dale L. Boger was given the Yamanouchi USA Faculty Award. Charles L. Brooks was elected a fellow of the American Association for the Advancement of Science, and Philip E. Dawson received a research fellowship in chemistry from the Alfred P. Sloan Foundation. Gerald F. Joyce was elected to membership in the National Academy of Sciences, one of the highest honors that can be conferred on a U.S. scientist or engineer. K.C. Nicolaou was awarded the Centenary Medal, Royal Society of Chemistry; Julius Rebek was named a fellow of the American Association for the Advancement of Science; and Peiqing Sun received the Ellison Medical Foundation New Scholar Award. In addition, K.C. Nicolaou, K. Barry Sharpless, and Chi-Huey Wong were named to a list of the world's most cited authors, who account for less than one half of one percent of all publishing researchers, for the past two decades.

I am obviously pleased with the progress of the Institute this year, and I continue to be inspired by the prodigious work, commitment, creativity, and enthusiasm of our extraordinarily talented scientists and administrative staff. In addition, our industrial collaboration agreement with Novartis continues to yield important research discoveries and has enabled TSRI to remain at the leading edge of scientific innovation. Also, we are most grateful to our Board of Trustees for their able guidance and to our donors for their ongoing support and strong belief in the importance of our work.



Richard A. Lerner, M.D.



K. Barry Sharpless, Ph.D., W.M. Keck Professor of Chemistry and member of The Skaggs Institute for Chemical Biology, was awarded the 2001 Nobel Prize in Chemistry.

Awarded annually by the Royal Swedish Academy of Sciences for achievements in physics, chemistry, medicine, literature, economics, and peace, the prize recognizes individuals who, as stipulated in Alfred Nobel's will, "have conferred the greatest benefit on mankind." The prize carries a cash award of about a million dollars.

Sharpless received this year's prize in chemistry along with William S. Knowles, formerly of Monsanto, and Ryoji Noyori of Nagoya University in Japan for "the development of catalytic asymmetric synthesis."

According to the prize committee, Knowles and Noyori shared half the prize "for their work on chirally catalyzed hydrogenation reactions." The other half of this year's award recognized Sharpless "for his work on chirally catalyzed oxidation reactions."

Sharpless contributed innovations to the development of broadly useful and commercially viable catalytic oxidation chemistry for the selective production of bioactive chiral molecules with the proper right- or left-"handedness."

Chirality, or handedness, is the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image. Proteins, DNA, and carbohydrates are all chiral molecules: without the correct handedness, they will not function as the basic molecules of life. Many drugs must also be of correct chirality; indeed, in some cases, the molecules with the wrong chirality can be toxic.

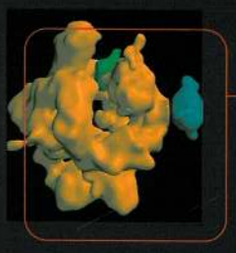
Sharpless's methods allow for the manufacture of safer and more effective antibiotics, anti-inflammatory drugs, heart medicines, and agricultural chemicals.

In 1980, Sharpless reported a breakthrough in synthesizing chiral molecules — the highly enantioselective epoxidation of allylic alcohols catalyzed by a titanium complex that is now used routinely. More recently, Sharpless developed another useful method, the asymmetric dihydroxylation of alkenes catalyzed by an osmium complex.

In fact, these processes, named the "Sharpless Asymmetric Epoxidation, Dihydroxylation, and Aminohydroxylation," have revolutionized organic chemistry by transforming asymmetric synthesis from nearly impossible to routine.

Sharpless received his B.A. from Dartmouth College in 1963 and a Ph.D. from Stanford University in 1968. In 1970, following postdoctoral studies at Stanford and Harvard Universities, he joined the faculty of the Massachusetts Institute of Technology. After three years at Stanford in the late 1970s, he returned to MIT as Arthur C. Cope Professor of Chemistry. He joined TSRI's faculty in 1991. Sharpless was elected to the National Academy of Sciences in 1985.

Other significant honors include the Tetrahedron Prize, the American Chemical Society's Award for Creative Work in Organic Synthesis and Arthur C. Cope Award; the Prelog Medal (Switzerland); the Janssen Prize (Belgium); the Scheele Medal (Sweden); the King Faisal International Prize for Science (Saudi Arabia); the Roger Adams Award in Organic Chemistry, American Chemical Society; the Harvey Prize of the Technion-Israel Institute of Technology; the National Academy of Sciences Award in Chemical Science; and most recently, the Wolf Prize in Chemistry and the Benjamin Franklin Medal. Also, he was listed among the "Top 75 Contributors to the Chemical Enterprise," in the 75 years since the founding of *Chemical & Engineering News.*



Three-dimensional structure of wild-type yeast RNA polymerase II, calculated from electron microscope images of single particles preserved in amorphous ice. Two subunits essential for promoter-directed initiation, Rpb4 and Rpb7, are colored in green and blue. Work performed in the laboratory of Francisco J. Asturias, Ph.D.

Cell Biology

SANDRA SCHMID, PH.D., CHAIRMAN

Like cells themselves, cell biology stands between the whole organism and its molecular pieces, linking an organism's genetic content and its physiology.

The Department of Cell Biology was founded ten years ago, and has since doubled in size. The department's scientists work on a range of problems, including trying to understand the structure of a single molecule and how it functions, looking at the complex machinery of the cell, and studying the integration of populations of cells into tissues and organisms, whole animal physiology, and complex behavior.

Understanding the operations of living cells leads to discovery of new therapeutic approaches to such ailments as cancer, heart, lung, muscle, retinal, and neurodegenerative diseases. The department takes a multi-tiered approach toward understanding the basic mechanisms behind these problems, combining the sophisticated tools of molecular and structural biology, chemistry, and genetics with traditional cell biology.

One example of this is the recent work of Benjamin Cravatt, Ph.D., who characterized an important enzyme that mediates the sensing of pain. When you feel pain, your brain releases a compound called anandamide, which provides some natural pain relief by binding to receptors on cells on the rostral ventromedial medulla, a pain-modulating center of the brain.

However, this effect is weak and short-lived as other molecules, particularly an enzyme Cravatt identified called fatty acid amide hydrolase (FAAH), metabolize the anandamide. FAAH may be an excellent target for pain therapy not only because it breaks down the natural molecules that provide pain relief but also because it seems that FAAH is the only enzyme responsible for doing so. The active site of FAAH is also unlike other similar enzymes, which may make it possible to block FAAH without repercussions elsewhere in the body.

Cravatt's hope is that controlling the action of FAAH could increase the longevity of anandamide and decrease pain.

Cravatt also directs the new Helen L. Dorris Institute for the Study of Neurological and Psychiatric Disorders of Children and Adolescents, which was recently established to uncover the pathological basis of neurological and psychiatric disorders and to enable the development of new therapeutic approaches. He will be leading the effort to recruit an interdisciplinary team of scientists to focus on understanding neuropathology in children and adolescents.

Other members of the Department of Cell Biology are developing and employing tools to watch molecular events in living cells in real time — and in the actual environments in which all genes and proteins interact.

VISUALIZING LIVING CELLS

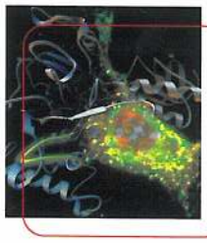
Klaus Hahn, Ph.D., has developed innovative fluorescent chemical dyes that can be attached to proteins to observe molecular signaling events that control cell migration in living cells — events otherwise impossible to see. When a specific biochemical reaction happens in a protein, the dye switches on. By following changes in the overall fluorescence of the cells with a microscope and a digital video camera, Hahn can observe protein conformational changes, binding, or posttranslational modifications.

Similarly, Clare Waterman-Storer, Ph.D., who co-developed a technique called fluorescence speckle microscopy, is able to watch the dynamics of microfilaments and microtubules. These fibers, which together constitute the cytoskeleton, are assembled from small subunits, actin and tubulin, respectively, and are critical for controlling cell shape, cell movement, and cell division. In this technique, tiny amounts of fluorescent chemical dyes are attached to the actin or tubulin subunits, which are then injected back into the cell and become incorporated into

Left to right:

Gerald F. Joyce, M.D., Ph.D., Professor, Departments of Molecular Biology and Chemistry, and The Skaggs Institute for Chemical Biology

Benjamin Cravatt, Ph.D., Assistant Professor, Department of Cell Biology and The Skaggs Institute for Chemical Biology



the microfilaments and microtubules as they grow. One can then illuminate the cells under a microscope and train a video camera upon them to capture the dynamics of the cytoskeleton. In essence, one can watch cells 'flex' their cytoskeletal muscles to learn how cells move, change shape, and divide.

Another powerful imaging technique used by cell biologists at TSRI is electron microscopy, which can produce three-dimensional maps of cellular structures. Recognizing and building on its world-renowned expertise in this area, TSRI is creating a center headed by Ron Milligan, Ph.D., that uses electron microscopy to create high-resolution structural images of large molecular complexes. Early next year, Milligan, together with his colleagues Drs. Francisco Asturias, Nigel Unwin, Mark Yeager, and Elizabeth Wilson-Kubalek, will move their groups into the newly constructed Center for Integrative Molecular BioScience (CIMBio). Here, TSRI will have the world's premiere center of high-resolution electron microscopy structural biology.

THE MOLECULAR MACHINES OF THE CELL

CIMBio seeks to combine the use of x-ray crystallography and electron microscopy to unravel the structures and mechanisms of action of the large molecular assemblies of the cell. These assemblies, rather than individual proteins, are the molecular machines of the cell — machines like the transcription complexes that make messages from the genes, membrane channels and pumps that import and export materials, and tiny motors that cause muscles to contract. The protein components of these machines may be studied by x-ray crystallography, and maps of the machines can be calculated from electron images. Combined with the x-ray structures of the components, this technique can yield a detailed description of the structure and action of the entire machine.

Two new recruits to the department, Associate Professors Bridget Carragher and Clint Potter, who are former co-directors of the Imaging Technology Group of the Beckman Institute for Advanced Science and Technology at The University of Illinois at Urbana — Champaign, are creating algorithms for automated data collection and analysis, which should simplify the technique of electron microscopy and allow throughput to be increased dramatically. As mathematical modelers, they are also developing algorithms to figure out the machinery of the cell. Cell structures interact with one another in a dynamic way, and the modeling tools of advanced mathematics are becoming more useful as more of the complexity of cells is understood.

Completion of the human genome has provided a list of the cell's interacting parts. The efforts of researchers in the Department of Cell Biology are focused on understanding how all of these parts work together to form a whole.

John Yates, Ph.D., a pioneer in the field of proteomics, is developing methodologies to look at protein expression changes in whole cells. Often the regulation of protein activity is controlled through post-translational modification and the interaction of one protein with another. Members of the Yates laboratory have developed sophisticated tools and computer programs to detect these subtle protein differences, and they hope that by comparing normal cells with cancer cells, they will identify potential weaknesses that can be targeted by drug therapy.

Bill Balch, Ph.D., is working to identify molecules involved in vesicle formation and trafficking through the cell as a way of addressing cystic fibrosis. Cystic fibrosis is caused by the aberrant synthesis and intracellular transport of a protein, called CFTR, essential for maintaining fluid balance in the lungs. By identifying and characterizing the cellular machinery and processing pathways for CFTR, Balch hopes to provide more effective avenues for treatment of the disease. Balch works in collaboration with other members of TSRI — especially those in the Department of Molecular Biology — to solve these structures.

The 1.04 Å structure of a-GDI, a protein that regulates membrane traffic, has a "mobile effector loop" (fluorescent green) that interacts with the Rab1 GTPase (green) and Syn5 (a fusion factor) (red) found together in pre-Golgi/Golgi compartments (yellow) (background image). Work performed in the laboratory of William E. Balch, Ph.D.

Sandra Schmid, Ph.D., has discovered a new enzyme belonging to the serine/threonine kinase family. Schmid has provided evidence that the enzyme regulates two types of cellular machines — the actin cytoskeleton and membrane trafficking — helping to spatially and temporally control cellular events.

In its first decade, the Department of Cell Biology has become a critical link between chemistry, structure, and cellular function. As scientists begin to study more complex cellular and organismal behavior, using ever more sophisticated methods, cell biologists will open new doors to the prevention, diagnosis, and treatment of human disease. ■

Chemistry

K.C. NICOLAOU, PH.D., CHAIRMAN

Members of the Department of Chemistry work at the interface of chemistry and biology. They conduct research in chemical synthesis, chemical biology, catalysis, combinatorial chemistry, and molecular design through interdisciplinary research that aims to discover the fundamental workings of human biology and to facilitate the drug discovery process.

This year, three members of the faculty, Drs. K.C. Nicolaou, K. Barry Sharpless, and Chi-Huey Wong, were included in the Institute for Scientific Information (ISI) list of the world's most cited authors in the past 20 years, comprising less than one half of one percent of all publishing researchers. According to ISI, the list identifies "individuals, departments, and laboratories that have made fundamental contributions to the advancement of science and technology in recent decades."

Shortly after this recognition, Sharpless won the 2001 Nobel Prize in Chemistry. The award also was presented to William S. Knowles, formerly of Monsanto, and Ryoji Noyori of Nagoya University in Japan, for "the development of catalytic asymmetric synthesis." Sharpless contributed innovations to the development of the selective production of chiral molecules with the proper right- or left-"handedness" — the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image. Proteins, DNA, and carbohydrates are all chiral molecules: without the correct handedness, they will not function as the basic molecules of life. Many drugs must also be of correct chirality; indeed, in some cases, the molecules with the wrong chirality can be toxic. One problem in designing pharmaceuticals is that a non-selective synthesis will yield both chiral forms, which may be hard or prohibitively expensive to separate.

In 1980, Sharpless reported a breakthrough in synthesizing chiral molecules with a method that is now used routinely, and he has since developed other methods that have revolutionized organic chemistry by transforming asymmetric synthesis from nearly impossible to routine. Sharpless's methods allow for the manufacture of safer and more effective antibiotics, anti-inflammatory drugs, heart medicines, and agricultural chemicals because they allow chiral forms to be synthesized selectively, rather than separated later.

COMBATING ANTIBIOTIC RESISTANCE

Chirality also played a role in a breakthrough reported by another laboratory this year. M. Reza Ghadiri, Ph.D., designed a broad approach for designing drugs to combat such problems as infections with antibiotic-resistant bacteria. Ghadiri and his coworkers created a class of biological polymers known as cyclic peptide nanotubes, which stack inside the cell membranes of bacteria and poke holes in their membranes, killing the bacteria.

In nature, only the L-form of amino acids (left-handed) are used to make peptides, or proteins, but there are no such constraints in the laboratory. Ghadiri and his colleagues built cyclic peptides by putting alternating right- and left-handed amino acids together into short six and eight amino acid chains, and then joining the two ends of the chain together. Because of their unusual alter-

Nanobiotic therapeutics. Disk-shaped cyclic peptides self-assemble inside bacterial membranes into hole-punching nanotubes that rapidly kill the bacteria. This new class of dynamic antibacterial agents selectively target a variety of bacterial pathogens including multidrug-resistant species. Graphics by Art Olson, TSRI. Work performed in the laboratory of M. Reza Ghadiri, Ph.D.

nating right- and left-handedness, these "cyclic" peptides are round and flat, like a donut.

By altering the amino acids from which the cyclic peptides were built, Ghadiri and his colleagues were able to design them so that they insert themselves into bacterial cell walls in a highly specific way. Inside the walls of a bacterium, these cyclic peptides spontaneously self-assemble into nanotubes, like donuts on a string.

These nanotube stacks have demonstrated strong bactericidal activity both in the test tube and in living tissue against a number of deadly pathogens, including multidrug-resistant *Staphylococcus aureus*, one of the most common hospital-acquired infections. Antibiotic-resistant bacteria are a growing public health threat worldwide, and the World Health Organization estimates the total cost of treating all hospital-borne antibiotic-resistant bacterial infections is around $10 billion a year.

ACTIVE SITE PROTEOMICS

In another avenue of research in the Department of Chemistry, two faculty members are collaborating to develop chemical methods that can be used to identify proteins whose activity is biologically important. The investigators, Benjamin Cravatt, Ph.D., and Erik Sorensen, Ph.D., call this method "active site proteomics."

Proteomics is a relatively new field that attempts to further the information available from the human genome by examining how and where genes are expressed inside a cell to make proteins. Insight into how the genome is expressed and how it is controlled can be found, for example, by comparing the expression profiles of two different cell types from different tissues, organisms, stages of development, or disease states.

However, at any given time cells will express more proteins than they actually use, and the proteins that are the most important may also be the ones that are the least expressed. What is often the predominant question in cancer research, for example, is which of these proteins are active — a question that active site proteomics seeks to answer by reading changes in protein activity directly and giving a visualization of the protein activity in a living cell by "interrogating" a protein's active site.

Cravatt and Sorensen have demonstrated that active site proteomics gives information on certain classes of enzymes. The researchers are currently developing broad chemical probes to apply the concept to a large menu of enzyme families. By characterizing the enzymes collectively rather than individually, a large number of enzymes in a cell can be profiled with only a few probes.

One of the principal uses of these probes will be to generate differential maps of cancerous and healthy cells. These maps should show the differences in activity between enzymes in the two types of cells — and may give clues that will be useful in developing cancer therapies.

Encoding proteins from DNA is one of the most fundamental requirements for life, since proteins do much of the microscopic work of the cell and make up a large part of the physical structure of cells and tissue. But one of the great unanswered questions of evolutionary biology is why there are only 20 amino acids in nature.

Peter Schultz, Ph.D., and his laboratory have developed a general method to make the bacterium *Escherichia coli* incorporate the novel amino acid O-methyl-tyrosine into proteins site-specifically and with high fidelity. This is the first of several new amino acids they are working on.

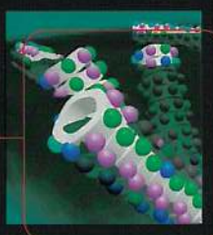
Also called "unnatural" because they are not among nature's original 20, these novel amino acids have the same backbone as the 20 standard amino acids but different side chains. Some have just slightly altered chemical structures and others have new functional groups added. In proteins, these differences may alter everything from structure and folding to activity. Certain "designer" side chains may even impart novel functionality.

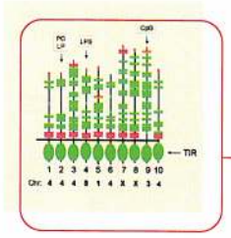
Proteins with novel amino acids may have enhanced or emergent properties and would be useful tools for studying protein interactions and cellular functions.

Left to right:

Michael McHeyzer-Williams, Ph.D., Associate Professor, Department of Immunology

Erik J. Sorensen, Ph.D., Assistant Professor, Department of Chemistry and The Skaggs Institute for Chemical Biology





Furthermore, having a bacterial expression system will make them trivial to produce on a massive scale.

The Department of Chemistry also continues to distinguish itself in the field of total synthesis of architecturally novel and biologically active natural products. By targeting these products, faculty members such as Drs. K.C. Nicolaou, Dale L. Boger, and Chi-Huey Wong hope to develop novel synthetic strategies and to create new synthetic technologies. Synthetic methods are crucial for drug development because they seek to take commercially available precursor chemicals and make, in abundance, compounds that cannot be found abundantly in nature. Indeed, several efforts are underway to synthesize antitumor, antibiotic, and antiviral agents. And almost every new synthesis may help facilitate further biomedical research. ■

Immunology

RICHARD J. ULEVITCH, PH.D., CHAIRMAN

All major diseases involve the immune system either directly or indirectly. Scientists in the Department of Immunology focus their research efforts on understanding the interactions of components of the immune system with pathogens, cancers, and each other.

Innate immunity is an ancient and powerful front line of the immune system whereby a rapid, non-specific response is mounted when a pathogen enters the body. One important area of research focuses on how the immune system responds to bacterial pathogens and what effect this response has on the body. Bruce Beutler, M.D., has identified the gene used by the innate immune system to help clear pathogens from the body. People with mutations in this gene have a higher-than-normal risk of contracting meningococcal sepsis.

Septic shock in general continues to be a major problem in U.S. hospitals. Richard Ulevitch, Ph.D., long ago recognized the importance of the CD14 protein in pathogen recognition, and his discoveries have provided the basis for a Phase III clinical trial that is currently testing anti-CD14 monoclonal antibodies as a therapy for septic shock.

Acquired immunity refers to the response that the immune systems of higher vertebrates mount against pathogens to eliminate infected cells and limit the spread of viruses or bacteria.

Immune cells of the thymus, or T cells, are one of the primary cell types responsible for acquired immunity. Jonathan Sprent, M.D., Ph.D., studies how T cells are formed in the virus and selected for their ability to recognize foreign invaders. Charles Surh, Ph.D., is studying how T cells develop and live when there is no pathogen in the body. Luc Teyton, M.D., Ph.D., studies the structures of important receptors used by T cells for immune recognition.

Wendy L. Havran, Ph.D., has found a completely new role for a population of T cells in the body called delta–gamma. These T cells arise early in development and reside in the skin and gut where, when the tissue surrounding them is traumatized, they secrete a particular growth factor that helps to recruit inflammatory cells. In mice without the cells or the growth factor, wound healing is delayed or missing completely. This work has important implications for skin inflammation, wound healing, and inflammatory bowel disease.

B cells are the other important player in acquired immune defense. David Nemazee, Ph.D., studies the mechanisms by which the body discriminates between self and non-self, and how B cells that are autoreactive can be salvaged and modified through a proofreading mechanism called receptor editing. Ann Feeney, Ph.D., studies the formation of the antibody repertoire, trying to determine which genes are used more than others and why.

The department is particularly well-known for its research on autoimmunity, in which a person's own antibodies or T cells target his or her own molecules, cells, or

Schematic illustration of the mammalian Toll-like receptor (TLR) family. The ten TLRs act as primary sensors of the innate immune system. Known specificities include: Lipopolysaccharide, LPS; peptidoglycan, PG: lipopeptide, LP; and unmethylated DNA CpG, unmethylated DNA. TLR genes are distributed on human chromosomes as shown by numbers at bottom. Work performed in the laboratory of Bruce Beutler, M.D.

tissues. Many of the most devastating modern diseases are caused by these immunological cases of mistaken identity.

Argyrios Theofilopoulos, Ph.D., has been working in this area at TSRI for 25 years. He has developed models for lupus, a complicated condition with a wide range of manifestations which afflicts approximately 1.4 million Americans. Theofilopoulos and Dwight Kono, M.D., have been working for several years to uncover the genes that contribute to the disease. They hope to use that knowledge to develop better, more targeted therapies than the current treatment, a regimen of non-specific drugs like cortical steroids, anti-inflammatories, and anti-malarials.

SIGNALING, CANCER, AND AUTOIMMUNE DISEASES

Tying the different parts of the immune system together are the scientists who study the signals cells exchange to communicate and carry out their work. Gary Bokoch, Ph.D., studies the signaling mechanisms that regulate how cells respond to their environment. This year, he reported the detailed mechanism of the regulation of an important enzyme, NADPH, that lies on the surface of white blood cells and destroys foreign pathogens. Wolfram Ruf, M.D., is looking for the signaling of enzymes of the blood coagulation cascade; Richard Klemke, Ph.D., is studying the basic molecular mechanisms that signal a cancer cell to metastasize.

Several researchers are interested in the potential for turning basic observations about the relationship between cancer and the immune system into new anti-cancer therapies. David Cheresh, Ph.D., has long led a program studying some of the molecules that contribute to the pathways of angiogenesis, the formation of new blood vessels. This formation is important for tumor growth, since the cancerous cells in tumors need the nutrients supplied by the new blood vessels to survive, and the cells themselves release chemicals that promote angiogenesis. Cheresh has looked at many ways of inhibiting this process and has devised some useful anti-angiogenics.

Ralph Reisfeld, Ph.D., has developed antibodies that target neuroblastoma tumors, the second leading cause of cancer in the United States after leukemia. One of his compounds is undergoing clinical trials at the National Institutes of Health.

TSRI is also home to one of the largest basic type 1 diabetes research programs in the world. Type 1, or insulin-dependent, diabetes is a chronic autoimmune disease that arises when T cells destroy the insulin-producing cells in the pancreas. Without insulin, the glucose in the bloodstream increases and is maintained at levels much greater than normal. Over time, this can lead to nerve and kidney damage, vision problems, and an increased risk of developing heart disease and vascular degeneration.

Linda Sherman, Ph.D., studies the killer T-cell repertoire and the rules that govern whether the T cells recognize "self" antigen or not. Susan Webb, Ph.D., looks at the regulation of helper T cells. Nora Sarvetnick, Ph.D., studies the causes and origins of type 1 diabetes with the goal of designing new therapies.

THE VIRAL DYNAMICS OF HIV

Several investigators in the department are molecular virologists. They aim to understand on a molecular level how viruses interact with host cells and the immune system. The department is well recognized for the efforts of its faculty to better understand the basic biology of HIV infection and the immune response to HIV.

Donald Mosier, M.D., Ph.D., has developed an elegant model to study HIV infection in living tissue. Using this model, researchers can test isolates from patients at various stages in the disease and look at how the replication and infectivity of the virus alters with mutations to its genome. They can also use the model to study basic biology and viral dynamics of HIV and to test

The x-ray structure of the multidrug-resistance transporter homolog MsbA from *Escherichia coli* modeled into the cell membrane. The transporter was solved to 4.5 angstrom resolution in the laboratory of Geoffrey Chang, Ph.D. MsbA is organized as a homodimer with each subunit containing six transmembrane α–helices and a nucleotide-binding domain. The view shown looks into the opening of the chamber, which catalyzes the flip-flop of substrates from the inner to the outer membrane leaflet.

the efficacy of vaccine and therapeutics candidates. Philippe Gallay, Ph.D., examines the role of host proteins in HIV infections.

HALTING PRION INFECTION

Dennis Burton, Ph.D., and Anthony Williamson, Ph.D., described an antibody this past year that clears prion infection in cell culture. Prions are like a molecular version of Dr. Jekyll and Mr. Hyde. The prion protein starts out with one shape that is innocuous, and ends up with another shape that is deadly. Prion infections are known to cause bovine spongiform encephalopathy (BSE), or mad cow disease, as well as one form of the same disease in humans, called variant Creutzfeldt-Jakob Disease. BSE itself is believed to have originated from a sheep form of the disease called scrapie.

Burton and Williamson originally developed antibodies to probe the structure and biochemistry of prion proteins. But one antibody they designed seems to halt the infection all together. Significantly, the normal cellular machinery degraded whatever infectious prions remained, suggesting that the antibody has the potential to cure established infection. This finding may lead to a treatment for mad cow disease and its human equivalent.

Of particular importance this year was the recruitment of Michael McHeyzer-Williams, Ph.D., one of the world's leading experts in flow cytommetry. He joins TSRI's faculty to pursue his interest in immune memory, particularly helper T-cell regulated B-cell memory.

On a final note, the department is pleased to recognize the contributions of Charles Cochrane, M.D., one of the original immunologists from the University of Pittsburgh. Cochrane celebrated his 40th year at the institute this year and continues to run an active laboratory. One of his noteworthy accomplishments is the development of a lung surfactant, which is in Phase III clinical trials as a treatment for infants with inflammatory lung problems. ■

Left to right:

Bruce E. Torbett, Ph.D., Assistant Professor, Department of Molecular and Experimental Medicine

Martin A. Schwartz, Ph.D., Professor, Department of Vascular Biology

Geoffrey Chang, Ph.D., Assistant Professor, Department of Molecular Biology

Molecular Biology

PETER E. WRIGHT, PH.D., CHAIRMAN

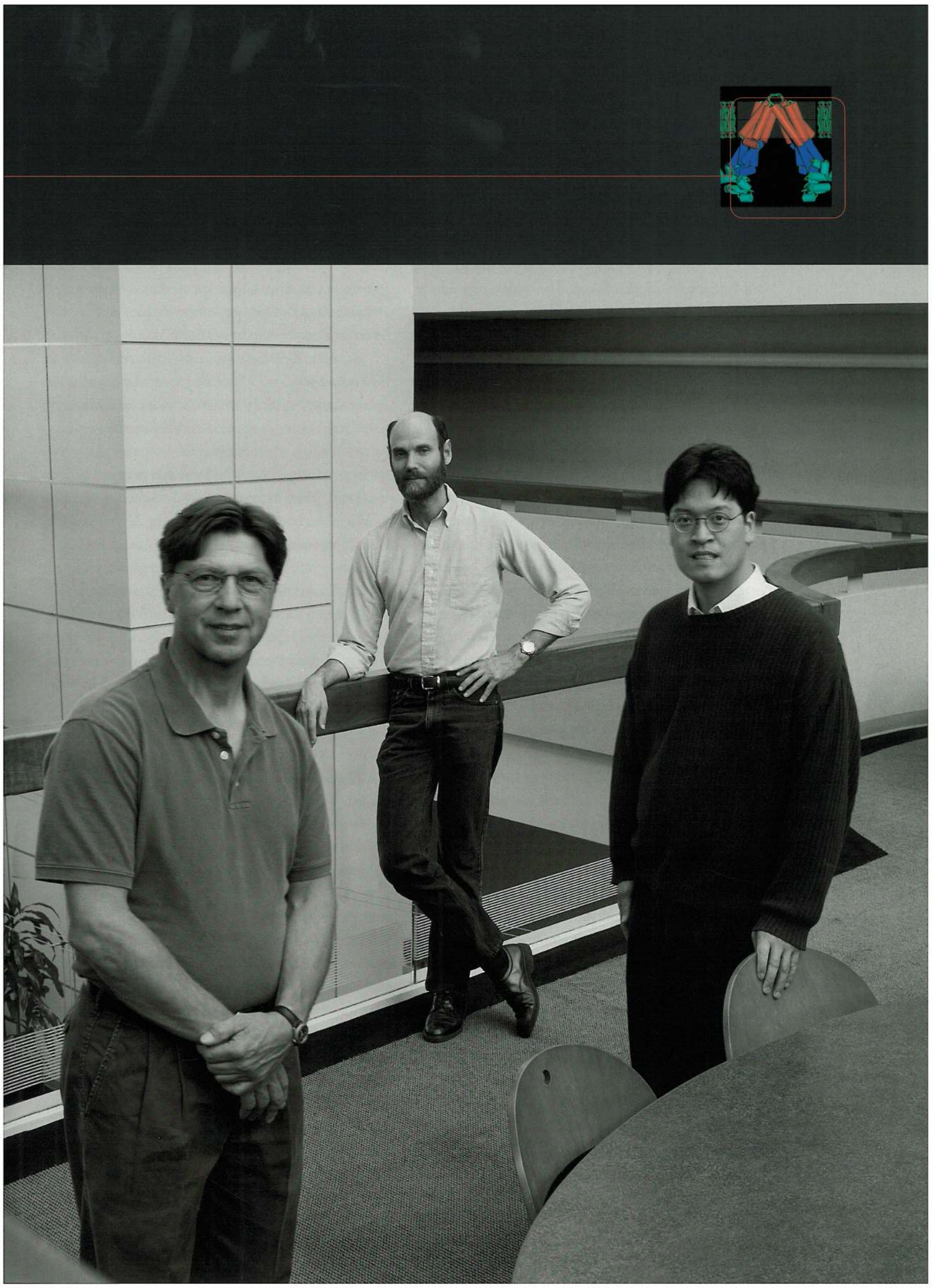
The structure of biological macromolecules by themselves and in assemblies continues to be one of the most compelling areas of research in molecular biology. Determining the three-dimensional structures of proteins and nucleic acids has led to a detailed understanding of the mechanisms by which these biological molecules function. This, in turn, provides important insights into the organism as a whole, disease states, and potential therapies to improve health.

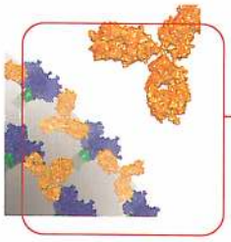
Moreover, the physiological role of these molecules, as observed through molecular genetics, provides important insights into disease states and how these states can be blocked or modified to improve health. Not surprisingly, many of the researchers in the Department of Molecular Biology are interested in the entire range of biology at the molecular level — from the most detailed structures to the broadest questions of molecular genetics.

A BREAKTHROUGH STRUCTURE

This year, Geoffrey Chang, Ph.D., solved an x-ray crystal structure that provides the first detailed glimpse of a membrane transporter protein. One of the ways that bacteria resist antibiotic drugs is by using membrane transporters, which are large proteins expressed in almost all organisms that sit in the cell membrane and move other molecules in and out. Harmful bacteria and certain cancer cells use these transporters to undermine the potency of antibiotics and chemotherapy drugs by pumping the drugs out before they have a chance to work.

Chang's structure is a breakthrough, opening the door for scientists to design a new class of drugs that patients would take in conjunction with antibiotic or chemotherapeutic agents to keep those drugs in the





cells and increase their efficacy. The work is particularly impressive, because membrane protein structures have been notoriously difficult to solve as they do not form good crystals, an important first step in solving a structure.

In another exciting finding, Ian Wilson, D.Phil., and his colleagues elucidated the structure of an antibody that effectively neutralizes human immunodeficiency virus (HIV). The structure will provide a basis for the design of vaccines against the HIV virus.

One of the most compelling medical challenges today is to develop a vaccine that will provide complete prophylactic protection to someone who is exposed to the virus. An important part of such a vaccine will be an effective neutralizing antibody against HIV, which would circulate through the blood, and track down and kill the virus. Normally, the antibodies that the body produces to fight HIV are ineffective because much of the surface of the HIV virus is inaccessible due to a coat of sugar molecules. However, the antibody solved by Wilson has a long finger-like region on its surface that penetrates the surface of the main viral glycoprotein gp120 on the HIV virus. The antibody neutralizes the virus, making it unable to invade cells and demonstrating that the human immune system is capable of raising antibodies that are effective against HIV.

Wilson also recently received a structural genomics pilot grant from the National Institutes of Health to establish a large-scale, multi-institutional consortium for research in this new discipline. The grant will enable Wilson and others to develop new technologies for high-throughput structure determination and should accelerate therapeutic drug design based on the knowledge reaped from the human genome.

Another major new initiative is being funded by the National Institute of General Medical Sciences and led by James Paulson, Ph.D. The NIGMS awarded the grant to Paulson to establish large-scale, multi-institutional consortia for research in the field of functional glycomics, the scientific pursuit of identifying and studying all of the carbohydrate molecules produced by an organism.

Functional glycomics aims to untangle huge biomedical problems like teasing apart the roles carbohydrates and proteins play in cellular communication. Some carbohydrates carry zip code-like addresses to help cells know where to go in the body, but the precise interactions between carbohydrates and proteins continue to mystify scientists, mainly because carbohydrates have proven to be extremely difficult to study. Unlike proteins, which are produced for the most part from a single template — an individual gene — carbohydrates are made by a cascade of chemical reactions inside our bodies. Many of these reactions are difficult to replicate in the lab. Paulson's Consortium for Functional Glycomics promises to change the face of this field by bringing together a large group of scientists from leading academic medical centers across the country.

A NEW INSTRUMENT AND A NOVEL AMINO ACID

The department also is a leader in nuclear magnetic resonance spectroscopy, a technique that enables scientists to determine the structure-function relationships of molecules. This summer, the most powerful, high-resolution nuclear magnetic resonance (NMR) spectrometer ever constructed was delivered to TSRI. Referred to by the frequency at which it operates, 900 MHz, this instrument is the centerpiece of the NMR structural studies at TSRI. With ten instruments at or above 500 MHz, the institute now has one of the most impressive NMR facilities in the world.

Paul Schimmel, Ph.D., and his coworkers have developed a novel approach to incorporating unnatural amino acids into proteins. *E. coli* mutants with a modified enzyme called valyl-t-RNA synthetase were selected experimentally. This enzyme attaches valine to the tRNA, which incorporates it into a protein. Using

IgG1 b12 potently neutralizes HIV by binding to protein spikes in the viral envelope and blocking attachment of the virus to human cells. (Antibodies are yellow and spikes are blue and green.) Work performed in the laboratory of Ian Wilson, D.Phil.

mutagenesis and screening, they were able to find a valine tRNA synthetase with no proofreading mechanism. Proofreading mechanisms are normally highly specific, allowing fewer that one mistake in 100,000. These mutants are capable of replacing a high proportion of the amino acid valine in cellular proteins with the unnatural amino acid, aminobutyrate, which is not among the 20 amino acids used by nature. The proofreading mutants were so good at missing mistakes that Schimmel and his colleagues report in their paper that 24 percent of all the valines were replaced with aminobutyrates. The method provides a powerful new tool for studying protein function and creates new opportunities for protein engineering because by using it, novel proteins with unusual chemical composition can be evolved and expressed in abundance.

These new proteins can now be purified and studied in isolation, or left *in vivo* and used as a probe to study cellular functions. Furthermore, the proteins with novel amino acids may prove to have enhanced or emergent properties. Having a bacterial expression system will make them easy to produce on a massive scale.

IMPORTANT PLAYERS IN MOLECULAR GENETICS

Important advances have also been made in the elucidation of the fundamental molecular processes involved in control of eukaryotic cell division. Cyclin E plays a key role in the cell cycle, functioning together with Cdk2 to regulate DNA replication and duplication of the centrosome. Proper timing of cyclin E expression and degradation is crucial; dysregulation of cyclin E levels is associated with genome instability and tumor formation. Steven Reed, Ph.D., and his colleagues have now identified a critical protein, termed hCdc4, which regulates cyclin E turnover by directing it to the cellular degradation machinery. Mutant forms of this protein occur in several tumor cell lines, suggesting that it may function as a tumor suppressor.

Another advance in molecular genetics came this year when Paul Russell, Ph.D., and Clare H. McGowan, Ph.D., identified the "resolvase" enzyme Mus81 from the fission yeast *Schizosaccharomyces pombe*, and its human analog. This is one of the most important enzymes involved in genetic recombination, and it may be responsible for generating genetic diversity during sexual reproduction.

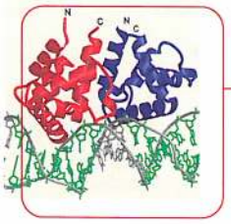
Genetic recombination occurs in the process of meiosis, when chromosomes from the mother and father become paired. Resolvase is essential for a crucial step in DNA recombination, because it is the molecule that allows two chromosomes to cross over. However, the DNA must at some point be uncrossed, which is the responsibility of resolvase enzymes.

The identification of a human resolvase may have a profound effect on cancer therapy because the enzyme also has an important role in cell replication. When cells are replicating their DNA prior to division, they have mechanisms to sense if the DNA is damaged. When the DNA is damaged, a cell's replication machinery will stop, spontaneously back up and form a Holliday junction. Resolvase recombines DNA strands at Holliday junctions and this allows the replication machinery to bypass the damaged DNA. Cancer cells are often defective in the mechanisms that sense damaged DNA. Russell and McGowan envision that treatment of tumors with chemotherapeutics that damage DNA, combined with rational targeting of resolvase activity, could be a highly potent cancer treatment. ■

Molecular and Experimental Medicine

ERNEST BEUTLER, M.D., CHAIRMAN

One of the great challenges of modern medicine is to understand how and why diseases manifest differently in different patients. Why do



some people with a genetic predisposition for a disease develop that disease while others don't? Why does a virus attack one patient aggressively while the same strain behaves in a relatively benign fashion in another? How does a genetic disease that comes from a single mutation in a single gene differ from person to person? And what are the mechanisms of diseases caused by multiple genes?

And the larger question is, of course, what can we do about these diseases?

With a staff of 50 scientists, the Department of Molecular and Experimental Medicine (MEM) encompasses a wide range of specialties and interests. The department was formed in the early 1980s and since that time has occupied a position at the interface of clinical and basic research. The mission that unites the department is the quest to understand the mechanisms of diseases and to devise strategies to improve health.

Though a number of its members have significant clinical experience, MEM is not a clinical department *per se*. Even so, MEM faculty are particularly interested in the clinical applications of their work.

One example is a program that tackles hepatitis B, a serious disease caused by a virus that attacks the liver. More than 350 million people worldwide, including 1.25 million Americans, suffer from the disease. Hepatitis B is the leading cause of liver damage and claims over a million lives a year worldwide.

But why are some patients able to rid themselves of the virus, while others continue to carry it and develop serious liver damage? Why do 15 to 25 percent of chronic sufferers die? Answers to these questions may lead to improved treatments.

Under the leadership of Frank Chisari, M.D., the department has become a world leader in the study of hepatitis, especially of the body's immune response to the disease. Chisari and his team of researchers study the immunobiology and pathogenesis of hepatitis B and related viruses in transgenic models and in infected patients.

Other researchers in the department are attempting to understand blood clots such as those that cause cardiovascular disease, particularly heart attacks and stroke.

STUDYING BLOOD CLOTTING AND ARTHRITIS

Zaverio M. Ruggeri, M.D., is conducting basic research to address the main disease-causing mechanisms responsible for arterial and venous thrombosis, the clotting of veins and arteries, and is laying the foundation for novel and more efficient therapeutic approaches. Ruggeri and his team study the interaction between vessels and blood platelets, the cell fragments that carry the chemicals the body uses in hemostasis, in which blood clots at a site of injury. Members of the Ruggeri lab are particularly interested in the structures of the adhesion proteins that mediate the formation of blood clots and the receptors on the platelets. Lab members have been solving the structures of these interacting molecules and piecing together how they work.

Such detailed knowledge of the three-dimensional structure of these adhesive proteins is indispensable for understanding the differences between normal hemostasis, where bleeding is stopped after a cut, and pathological thrombosis, in which a clot of platelets occludes blood flow and causes cardiovascular disease.

Another serious disease, arthritis, is the topic of research in a laboratory headed by Martin Lotz, Ph.D. Osteoarthritis is the most common form of the disease and arises from the degeneration of cartilage in joints. Lotz, who heads the MEM's division of arthritis research, studies cartilage and investigates how one can influence its growth.

Joint trauma, for instance, is a known risk factor for osteoarthritis, but there are no pharmaceuticals to limit this tissue damage. Using models of cartilage injury, Lotz and his team have found that apoptosis, or programmed cell death, can be induced by mechanical stress in joints, and they are testing inhibitors to see whether

The fDNA complexed structure of the key transcription factor initiating development in sporulating bacteria. Work performed in the laboratory of K.I. Varughese, Ph.D.

they can decrease progress to osteoarthritis. Lab members are also looking at the stimulation of cartilage damage by chemical signals released by immune system cells and investigating whether blocking these signals represents a viable approach to preventing osteoarthritis.

In another line of research with clinical implications, Ernest Beutler, M.D., and other members of the department have collaborated with Kaiser Permanente on the largest DNA study in history. Recently completed, this epidemiological study examined the DNA and clinical data of some 41,000 patients for genetic susceptibility to a disorder known as hereditary hemochromatosis. Hemochromatosis is a metabolic disorder in which excess deposits of iron occur in the liver, pancreas, and other organs. Among other manifestations, cirrhosis of the liver, diabetes, and cardiovascular diseases may result.

Although it was originally thought that most people with the mutation that causes hemochromatosis were symptomatic and suffered a high mortality rate if untreated, the results of the study show clearly that very few manifest the disease. Most who are homozygous for this genetic mutation seem to enjoy a normal life span. This study may lead to a rethinking of the cost-benefit of screening normal populations for this disease and of the importance of its early treatment.

Investigators in the department are also participants in the Scripps Cancer Center with physicians from Scripps Clinic and the ScrippsHealth system, institutions which together treat 25 to 30 percent of all the cancer patients in the San Diego area. The cancer center's goal is to facilitate the development of new cancer drugs from their beginnings in the laboratory to their final approval for use by cancer patients. This program will enable researchers to contribute more directly to the solutions they seek by moving potentially useful laboratory findings quickly and seamlessly into the clinic through their close collaboration with clinical staff. ■

Neurobiology

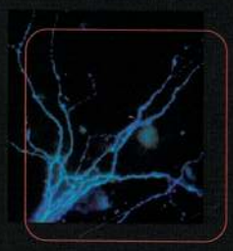
GERALD M. EDELMAN, M.D., PH.D., CHAIRMAN

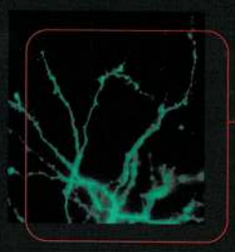
The Department of Neurobiology is a highly focused, multidisciplinary department seeking to understand molecular, cellular, and chemical aspects of the development and function of the nervous system. It brings to bear all the modern techniques of biology and chemistry to do so.

One important question in the development and morphology of the nervous system is how collectives of interacting cells and cell products give rise to the complex connectivity of the brain. The department has long had a program studying the effect of cell adhesion molecules (CAMs) on cells in the central nervous system. The neural cell adhesion molecule (N-CAM) was the first CAM to be characterized. It was discovered in 1978 in the laboratory of Gerald Edelman, M.D., Ph.D. N-CAM mediates cell-cell interactions in development and in adult tissues, and its binding induces a variety of intracellular signals, including those leading to changes in gene expression.

A number of the department's faculty study the effect of CAMs on morphogenesis. Bruce A. Cunningham, Ph.D., looks at the structure and function of CAMs by using biochemical and molecular biological techniques to examine the interactions of the domains or parts of N-CAM. In collaborative studies, he is also examining the three-dimensional structures of the domains using nuclear magnetic resonance.

Frederick S. Jones, Ph.D., and Robyn Meech, Ph.D., investigate the regulation of CAM genes, and the effect of this regulation on neural morphogenesis. They study the regulatory regions of the CAM genes and transcription factor families like the Hox and Pax proteins, which regulate CAM expression. In recent years, together with Edelman, they have designed and used a new method for constructing synthetic promoters to study transcription in different cell types and states. They have also obtained





In situ analysis of an internal ribosome entry site in the 5' untranslated region (UTR) of RC3, a dendritically-localized mRNA. Shown are fluorescent photomicrographs of dendrites from hippocampal neurons expressing mRNAs that encode both cyan (ECFP) and yellow (EYFP) fluorescent proteins. mRNAs with the b-globin 5' UTR between cistrons express ECFP and appear blue, while those with the RC3 5' UTR express both cistrons and appear turquoise. Work performed in the laboratory of Vincent P. Mauro, Ph.D.

direct evidence that CAM-mediated adhesion itself can influence gene expression.

Kathryn L. Crossin, Ph.D., and her colleagues made an important discovery last year. They found that by adding N-CAM to neural stem cells, the stem cells can be transformed into neurons. When they put the stem cells together with N-CAM, the stem cells developed into neurons in the normal several week span that development takes in a test tube, and at the end of this period the neurons began to fire.

This result may one day point the way to novel treatments for a number of neurodegenerative diseases by suggesting a method to regenerate neurons. Cellular therapy, in which neural stem cells are implanted to treat conditions like Parkinson's disease, has shown only limited success because most of the implanted cells don't become neurons. But Crossin and her colleagues were able to bias these stem cells to become neurons — *in vitro* — as high as 90 percent of the time. Therapy aside, this work has also provided a wealth of follow-up topics, such as determining the mechanisms that influence the emergence of firing activity.

CONTROLLING PROTEIN SYNTHESIS

Another important area of research has been the control of protein synthesis by ribosomes — the molecular machines that synthesize proteins from messenger RNA (mRNA). When genes are expressed, they are first transcribed into an mRNA, which then is transported to another part of the cell where it is translated into protein. Protein synthesis occurs when a ribosome "reads" an mRNA and uses it as a template to synthesize a protein chain. But nothing in life is ever that simple.

Ribosomes must interact with mRNAs to function, and these interactions are controlled by initiation factors. The initiation factors, conglomerating around a "cap" consisting of a methylated guanosine-nucleotide on the end of the mRNA strand, attract all but the larger subunit of the ribosome to the mRNA, and move to the first three-letter codon, which says "put amino acid X here." Once there, the larger ribosomal subunit is recruited and begins to make proteins.

Vincent P. Mauro, Ph.D., and his colleagues have highlighted a further level of control of this highly regulated molecular factory — internal sequences in the untranslated or non-protein coding regions of mRNA that can recruit the ribosome.

These so-called internal ribosomal entry sites (IRESes) are small stretches of nucleotides contained within the mRNA molecules that can help attract ribosomes. They appear to do this because the nucleotides in the IRESes are complementary to corresponding nucleotides in the ribosome, much of which is also RNA. The IRES RNA binds to the ribosomal RNA through base pairing, similar to the way that two strands of DNA bind to each other.

Mauro and his colleagues found that multiplying the number of small IRES-modules in an mRNA resulted in a large increase in protein translation and a dramatic increase in the protein generated. This tremendous amplification of output may have potential applications in gene therapy and in biotechnology.

His work also suggests a more sophisticated way of understanding the translation of genetic messages. In this model, there are enhancers and inhibitors within the mRNA that influence protein synthesis. Different mRNA molecules with different IRES combinations may form a competing population for translation, allowing the cell to preferentially translate one message over another.

The overall goal of the department is to understand the fundamental molecular and cellular mechanisms that regulate neural development. There is no focus on a particular disease or pathological condition, but the studies of these scientists have significant implications for the diagnosis and treatment of a wide range of diseases. ■

Left to right:

Vincent P. Mauro, Ph.D., Assistant Professor, Department of Neurobiology

Kathryn L. Crossin, Ph.D., Associate Professor, Department of Neurobiology

Neuropharmacology

FLOYD E. BLOOM, M.D., CHAIRMAN

Alcohol, nicotine, drug addiction, depression, and viral infections are all noteworthy for the cost they inflict upon individuals and society. The direct and indirect public health costs of alcoholism are estimated to be in the hundreds of billions of dollars yearly. More than half a million Americans die each year from smoking-related illnesses. In any given year, one out of every ten people in the United States suffers through some form of major depression. And more than three quarters of a million people in this country have AIDS, which can have major deleterious effects on the brain.

The Department of Neuropharmacology addresses these disorders, exploring the function of the normal and diseased brain and establishing the fundamental mechanisms by which the environment and genes lead to various disorders of the brain. Some department scientists study the mechanisms of neuronal synaptic communication to determine the difference between normal signaling and signaling in AIDS patients or those who are dependent on alcohol, marijuana, cocaine, morphine, tobacco, or other drugs. Others focus on various aspects of the brain's chemicals, molecules, or cells to achieve a better understanding of how to devise effective treatments for these conditions.

The department has a large program to study the effect of HIV on the brain, a debilitating but often overlooked aspect of the disease. One quarter to one third of all AIDS patients suffer from some form of central nervous system disorder during the course of their infection, ranging from minor cognitive and motor disorders to severe dementia, symptoms collectively known as neuroAIDS. These problems are the direct result of the inflammation brought on by the immune cells coursing through the brain. This inflammation interferes with neuron signaling, slowing down the processes within the cerebral cortex, the part of the brain responsible for higher brain functions such as thought, sensation, voluntary muscle movement, reasoning, and memory.

In order to further research the cause, prevention, and treatment of HIV infection in the brain, Howard Fox, M.D., Ph.D., has organized the Scripps NeuroAIDS Preclinical Studies Center, funded last year through a $10 million grant from the National Institute of Mental Health. The center brings together researchers from throughout the institute to look at all neurological aspects of HIV infection and treatment. Fox himself has developed an experimental model of an HIV-like virus to establish the molecular and cellular basis of neuroAIDS pathogenesis.

VIRUSES AND THE BRAIN

Several other researchers in the department conduct programs that investigate how viruses get into the brain and how they cause disease. Michael B.A. Oldstone, M.D., studies the mechanisms of immune system interactions that mediate the pathologic effects of viral infection in the central nervous system. He also directs a multiple investigator initiative sponsored by the National Institute on Aging, investigating the role of viruses in brain pathology. Michael Buchmeier, Ph.D., studies the ability of hepatitis virus to remove myelin, the sheath surrounding nerve fibers, as an experimental model of human multiple sclerosis. Lindsay Whitton, M.D., Ph.D., studies the molecular and immune mechanisms involved in viral pathogenesis and antiviral immunity. He is also working on approaches to vaccinate against viral diseases using DNA.

The department also has a strong program in alcohol research. Many questions remain to be answered in this field. For instance, we know that the children of alcoholics are four to five times more likely to become alcoholics

In addition to immune deficiency, AIDS is also associated with brain infection by HIV. Infiltrating immune cells can act in concert with brain support cells to produce neurotoxic products, compromising the central nervous system. Work performed in the laboratory of Howard Fox, M.D., Ph.D.

themselves, but we do not know the neurological basis for this trait.

THE LONG-TERM EFFECTS OF ALCOHOL ON THE BRAIN

For more than 20 years, TSRI's alcohol research center has been investigating the long-term effects of alcohol on the brain. Recently, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) funded a multi-year consortium headed by researchers at TSRI to identify the molecular basis of alcoholism. The Integrative Neuroscience Initiative on Alcoholism, directed by George Koob, Ph.D., aims to address the basic science of alcoholism and to establish a platform upon which future treatments can be built. Identifying the nature of the neuron transmitters that addictive drugs act on makes it possible to design new therapies to interrupt those effects and blunt the influence of the drug.

Cindy Ehlers, Ph.D., studies the role of genetic factors and their interactions with brain motivational circuits in alcoholism. Understanding motivational circuits is critical to understanding drug abuse and the brain. Many drugs act as natural neural transmitters, turning on what is known as the reward system within the brain and making the drug user feel good. Drug dependence often develops because of these internal rewards.

Several researchers study the basis of this system of reward and motivation. Koob has conceptualized drug dependence as an allostatic break with homeostasis where the brain reward system becomes progressively dysregulated and where residual neuropharmacological changes persist post-dependence. Athina Markou, Ph.D., investigates the neurobiology of reward as it relates to drug abuse, depression, and schizophrenia. John Polich, Ph.D., uses electrophysiology to look at the role of drugs and the neurotransmitters they affect in altering human cognition. Friedbert Weiss, Ph.D., studies brain motivational circuits and their connections in animal models of drug craving and relapse. George Siggins, Ph.D., works on the interactions of drugs of abuse, such as amphetamines and alcohol, with the neuropeptide systems in the brain's reward pathways. Steve Henriksen, Ph.D., also studies the basis of reward, and directs a program looking at methamphetamines as a drug of abuse.

Many investigators in the department are interested in the effect of the body's own substances on the brain. Donna Gruol, Ph.D., studies the role of calcium signaling in regulating neuronal functioning and development. She also researches signaling related to the presence of cannanbinoid-containing drugs like marijuana. Merrill Mitler, Ph.D., examines the role of neurotransmitters and cytokines in disorders of sleep and waking. Iain Campbell, Ph.D., studies the role and mechanisms of action of cytokines and chemokines in the brain in inflammatory states.

Tamas Bartfai, Ph.D., studies molecular and cellular correlates of changes in cognition, long-term memory, and emotional states. Bartfai also directs the Harold L. Dorris Neurological Research Center, founded in 1999 with a remarkable $10 million endowment from Helen L. Dorris of San Diego. The center provides education and conducts research into neurological disorders, including schizophrenia and Alzheimer's disease, as well as advancing knowledge of the process of aging of the brain.

Understanding the link between the physiology of the brain and behavior is a key goal of all the investigators in the department, as is turning these basic observations into useful therapeutics for degenerative diseases, emotional disorders, and drug abuse. ■

The Skaggs Institute for Chemical Biology

JULIUS REBEK, JR., PH.D., CHAIRMAN

During the last two decades, scientists have begun to understand the molecular basis of disease in terms of malfunctioning protein and

The medium is the message. Four copies of a single molecule recognize each other and self-assemble through hydrogen bonds into a capsular framework that surrounds a guest molecule. Such molecular capsules exercise control over the chemical environment and collisions experienced by the guest molecule. Encapsulation within this medium can give rise to a wide variety of emergent properties, including chiral selection, transduction of optical signals, polymerization, catalysis, and the stabilization of reactive species. Work performed in the laboratory of Julius Rebek, Ph.D.

nucleic acid molecules. This has resulted in new therapies, small molecule drugs that are specifically directed to correcting the malfunctioning molecules. However, long before such drugs can be designed, specific questions need to be answered for each disease: Where are the malfunctioning molecules? What are their structures? How do they operate? Can we make drugs to influence them? If so, how do the drugs and the targets interact? These questions bring together the disciplines of structural biology, cellular biology, catalysis, organic synthesis, and molecular recognition — the range of disciplines investigated by researchers at The Skaggs Institute for Chemical Biology.

The institute was established in 1996, made possible by a commitment of $100 million from Aline and L.S. Skaggs through the Skaggs Institute for Research and their family foundation, the ALSAM foundation. In the last five years, Skaggs investigators have determined the structures and functions of many proteins and nucleic acids, particularly those involved in cancer and diseases of the immune system; they have invented new methods for the synthesis of small and large molecules; and they have discovered new catalysts for chemical reactions of interest to medicinal chemistry.

WINNER OF THE NOBEL PRIZE

This year, those at the institute celebrated the award of the 2001 Nobel Prize in Chemistry to one of its members, K. Barry Sharpless, Ph.D. Sharpless was given the prize for his development of methods for the selective synthesis of chiral molecules. Chirality is the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image — its right- or left- "handedness." Proteins, DNA, and carbohydrates are all chiral molecules: without the correct handedness, they will not function as the basic molecules of life. Many drugs must also be of correct chirality; indeed, in some cases, the molecules with the wrong chirality can be toxic.

In 1980, Sharpless reported a breakthrough in synthesizing chiral molecules with a method that is now used routinely, and he has since developed other methods that have revolutionized organic chemistry by transforming asymmetric synthesis from nearly impossible to routine. Sharpless's methods allow for the manufacture of safer and more effective antibiotics, anti-inflammatory drugs, heart medicines, and agricultural chemicals because they allow chiral forms to be synthesized selectively, rather than separated later.

Several Skaggs investigators synthesize molecules that may have the potential to be used in the clinic. Two members of The Skaggs Institute, K.C. Nicolaou, Ph.D., and Dale Boger, Ph.D., have, together with their research teams, successfully completed the total synthesis of vancomycin, which acts as the last line of defense against life-threatening antibiotic-resistant infections.

The last decade has seen the emergence of a strain of *Staphylococcus aureus* that is resistant to vancomycin's mode of action, in which the molecule binds to the cell wall of a bacteria and arrests its growth. *Staphylococcus aureus's* resistance involves a subtle, single-atom change in the components of the growing cell wall. The resistance is encoded in the DNA of the organism and this DNA is mobile — it can be passed from one bacterial cell to another, similar to the way in which penicillin resistance spreads. Researchers at The Skaggs Institute are positioned to overcome this resistance. Boger's group is making the complementary changes on the synthetic vancomycin, hoping to restore the binding to the bacterial cell wall and overcome the resistant bacteria's defense.

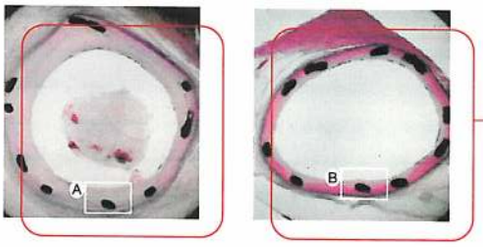
Nicolaou's lab is taking a different approach to overcoming antibiotic resistance. Using the methods known as combinatorial chemistry, a large number of vancomycin-like molecules are being prepared and screened for antibiotic activity in a short time.

Another member of The Skaggs Institute, Chi-Huey Wong, Ph.D., has also used the combinatorial technique to overcome bacterial resistance. By binding two molecules

Left to right:

Howard S. Fox, M.D. Ph.D., Associate Professor, Department of Neuropharmacology

George F. Koob, Ph.D., Professor, Department of Neuropharmacology



of the aminoglycoside antibiotic family to each other at different distances, he has made molecules that show potent activity against infectious organisms.

New treatments for pain, especially chronic pain syndromes, are desperately needed. The research group of Benjamin Cravatt, Ph.D., is dedicated to identifying, characterizing, and validating new targets for the treatment of chronic pain. Opioid-based molecules like morphine are effective for treating acute pain following injury, but this approach has failed to provide relief from persistent pain that results from neural damage and/or chronic inflammation. These clinical shortcomings arise because the human receptors — the targets of opioid drugs — become unresponsive or desensitized in situations of persistent pain, and morphine and related opioid-based therapeutics are addictive. The Cravatt group has recently determined that the brain enzyme fatty acid amide hydrolase (FAAH) is a novel target for the treatment of pain.

Members of the Cravatt lab isolated and genetically manipulated the key proteins involved in neural pain pathways and showed that FAAH is responsible for regulating the levels and activities of a family of neural signaling molecules called fatty acid amides. When these fatty acid amides are present, pain sensations are reduced. Cravatt's group found that if one eliminates FAAH, fatty acid amides accumulate naturally and signal to reduce pain without affecting motility or cognition systems. These exciting results argue that chemical inhibitors of FAAH may provide the much sought-after relief of chronic pain without inducing addiction (as seen with opioids) or motility/cognitive defects (as seen with marijuana).

BLOCKING COCAINE TO FIGHT ADDICTION

The Skaggs Institute currently has one potential therapy scheduled to go into human clinical trials. Licensed by Drug Abuse Sciences of Mountain View, CA, the antibody was developed by the laboratory of Kim Janda, Ph.D., as a vaccine to prevent cocaine from reaching the brain.

Normally, brain levels of cocaine rise rapidly once it is taken into the system. The drug accumulates in the ventral tegmental area of the brain, which is connected by nerve cells to the nucleus accumbens, the brain's so-called pleasure center. There, the cocaine molecules interfere with the normal regulation of dopamine by binding to dopamine transporters and blocking them from recycling the neurotransmitter. This produces a euphoric feeling in the user — a quick rush that hits seconds after taking the drug and lasts several minutes. These vaccines suppress this euphoria and, therefore, the reinforcing aspects of the drug.

Interestingly, unlike other types of treatment, the vaccines developed by the Janda lab do not interfere with the neurological targets of the drug, but instead help the body keep cocaine from ever reaching the brain. The vaccines do this by inducing an active immune response that creates antibodies against cocaine in the bloodstream. If an addict later takes a hit, the antibodies will clear the cocaine from the system.

These examples show how understanding the scientific underpinnings of a medical problem can lead to therapies. Many of these scientists' projects represent radically new ways of thinking and could not have drawn support from traditional funding sources.

The Skaggs Institute also seeks to provide a nurturing environment for the next generation of research scientists. To further this goal, the institute has established the Skaggs Predoctoral Fellows Program and the Skaggs Postdoctoral Fellows Program. The Skaggs Fellowships were created to grant financial support, further the careers of young men and women at TSRI, and provide tomorrow's leaders in drug development. Awards will be given to the best and brightest students who show outstanding promise in chemical biology research as it relates to human health. ■

A DNA enzyme, developed in the Joyce laboratory, prevents re-narrowing of the coronary arteries following angioplasty. Figure A shows a cross section of the coronary artery from a pig that underwent angioplasty. Figure B shows the same view from an animal that had been treated with the DNA enzyme. Note the thicker vessel wall in A. (From Lowe et al., Circ. Res. 89:670, 2001.)

Vascular Biology

DAVID J. LOSKUTOFF, PH.D., CHAIRMAN

Diseases of the coronary and cerebral arteries account for more than half of all deaths in Western societies, and the cost of managing vascular disease in the United States alone is more than $100 billion annually. The growing realization that vascular cells also play a critical role in the growth of tumors and a variety of inflammatory disorders suggest that the real cost of vascular disease may be even higher. The Department of Vascular Biology applies basic principles of cell biology, chemistry and genetics to study the development, structure and diseases of the vascular system.

A common goal of the work is to define the molecular basis for the very specific interactions between vascular cells, components in the blood, and the extracellular matrix. These interactions are essential for normal cell growth, movement, and differentiation, and represent the most fundamental processes in biology. Department members study how the interaction between specific integrins and proteins in the cytoplasma and extracellular matrix of cells regulate vascular cell growth and behavior. Integrins are a family of adhesion receptors on cells, and the focal point for cell matrix-interactions. When a ligand — an organic molecule that bonds with other molecules to form more complex structures — binds to its integrin receptor, it sets off a signaling mechanism inside the cell and creates a chemical reaction that causes the cell to change shape, move, etc. This chemical information is carried from the extracellular matrix through the integrin receptor into the cell, and results in changes in cell structure and function. Researchers in the department are working to unravel the molecular details and delineate the signaling pathways that govern integrin-mediated events in vascular cells.

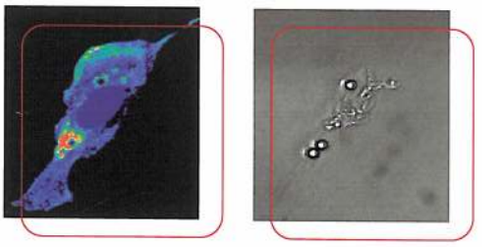
They also seek a more complete understanding of the various roles of complex protease cascades in the control of vascular cell function. Proteases are enzymes that can degrade and destroy other proteins, including those present in the extracellular matrix and those that form blood clots. Those currently under investigation include the plasminogen activator system, matrix metalloproteinases, and cell death (apoptosis) proteases. A single molecule of a very specific protease, for example, can activate the entire blood-clotting cascade, ending with the formation of hundreds of thousands of clot-forming prothrombin molecules, an elegant and exquisitely regulated process.

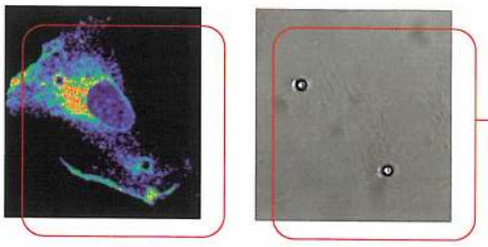
On the other hand, t-PA is a protease that can dissolve clot proteins and restore normal blood flow. Raymond Schleef, Ph.D., has employed genetic engineering to introduce t-PA into leukocytes, or white blood cells, and then insert them into rats. These protease-modified leukocytes go directly to existing blood clots in the rat circulatory system and dissolve them. This may be a new and more efficient way to deliver therapeutic proteases to sites of disease and injury.

Proteases also are frequently expressed in abnormal pathological situations. For example, certain types of invasive cells, including many cancer cells, use proteases to cut through tissue barriers during metastasis. Abnormal expression of certain protease inhibitors by vascular cells may increase the risk for heart attack under certain conditions, including obesity and type II diabetes, because the proteases that normally remove pathological clots no longer function. A lack of protease inhibition, however, can lead to bleeding problems due to the premature removal of normal clots.

REGULATION OF NEW BLOOD VESSEL GROWTH

Another area of research includes investigation into the mechanisms that regulate angiogenesis, the growth of new blood vessels, with a focus on integrins and proteases/protease inhibitors. These studies provide new insights into vascular diseases including tumor angiogenesis, arteriosclerosis, stroke, thrombosis, restenosis and hypertension, and bleeding.





During the past year, several scientists in the department have achieved recognition for their innovative research efforts and have attained increasingly prominent roles in national and international symposia. In addition, funding for vascular biology research at TSRI by the National Institutes of Health continues to grow at an accelerated rate.

Two new faculty members have been recruited to the department this past year, James Quigley, Ph.D., and Heidi Stuhlmann, Ph.D. Quigley, formerly a professor in the Department of Pathology at the State University of New York in Stony Brook, brings with him a longstanding interest in the biochemistry and cell biology of proteases and their inhibitors in cancer and angiogenesis. Stuhlmann, from the Mt. Sinai School of Medicine in New York, is a mouse developmental biologist interested in the early development of the vascular system. She has identified a novel gene that appears to be important for vascular development in the mouse embryo.

The past year was extremely successful in terms of scientific accomplishments, the maturation of ongoing projects, and the development of new avenues of research. ■

Graduate Studies Program

JEFFERY W. KELLY, PH.D., DEAN

At the annual Board of Trustees meeting, Jeffery W. Kelly, Ph.D., was named dean of the Graduate Studies Program. He had been named acting dean in September 2000 upon the untimely death of the program's first dean, Norton B. Gilula, Ph.D.

This year marks the 12th year of the Graduate Studies Program and the conferral of the 100th doctoral degree. The continuing interconnection between the graduate program and the institute provides the program's strength and is one of the true measures of its success.

To make classes more rewarding to students, the course directors reorganized course content. In addition, some of the elective courses in the macromolecular and cellular structure and chemistry (MCSC) program were integrated into the core curriculum. The directors also decided to allow students to receive credits for units taken in either the MCSC program or the chemistry program. Thus, students can benefit from developing a more interdisciplinary background.

Although research is the major component of Ph.D. programs at other institutions, the emphasis on research at TSRI is unusually strong, underscoring the synergy between the missions of both TSRI and the graduate program. Students in the MCSC program finish as well-equipped problem solvers; nearly 70% enter academia upon graduation, and 30% are recruited to work in industry. Students on the chemistry track graduate with the skills to become bio-organic or synthetic chemists. Approximately 40% obtain positions in the pharmaceutical and biotechnology industries; the remaining graduates become involved in academic research. Irrespective of the environment they choose, TSRI graduates are recruited to fill highly competitive positions in academia, government, and industry.

Over the years, the Graduate Studies Program has enhanced its competitive edge by recruiting highly qualified students from various disciplines and with diverse scientific interests. This year we recruited 24 chemistry students and 14 MCSC students from a wide range of undergraduate universities.

At commencement ceremonies held in May, TSRI conferred doctoral degrees on 21 students. Christopher N.C. Boddy, Dennis T.Y. Bong, Steven L. Castle, Joel Goldberg, Kathryn M. Koeller, H. Michael Petrassi, Allen A. Thomas, Jonathan D. Toker, and Yohei Yokobayashi received degrees in chemistry. Danuta Balicki, Phyllis Frosst, David J. Hosfield, Kinya Hotta, Nicole Kresge, Ryan S. Littlefield, Satchidananda Panda, Matthew P. Matricelli, Christopher D. Putnam, Erica Ollmann Saphire, Vickie Tsui, and Jacques T. Weissman

Cells were treated with small beads coated with an adhesive protein, fibronectin, that binds to integrin receptors (left), or with anti-integrin antibody (right). The beads can be seen in the gray images. Cells were then imaged using a new technique that visualizes where the signaling protein Rac interacts with a target protein. Red/yellow shows high levels of interaction, blue shows low. The results demonstrate that integrins locally enhance the interaction of Rac with its target protein. The work, performed in the laboratory of Martin A. Schwartz, Ph.D., demonstrates a novel mechanism by which adhesion of cells to connective tissue proteins regulates their behavior.

were granted a degree in macromolecular and cellular structure and chemistry. Joseph Graham Davis, Jr., governor of the State of California, received an honorary doctor of science degree.

As in years past, students obtained financial support from a broad range of prestigious sources, including the Skaggs Institute for Research, Howard Hughes Medical Institute, National Science Foundation, La Jolla Interfaces in Science, Medical Research Council of Canada, American Heart Association, American Chemical Society, United Negro College Fund, National Institutes of Health, Natural Sciences and Engineering Research Council of Canada, the Roche Award, and the Hewitt Award.

We are also grateful to our generous donors: the Achievement Rewards for College Scientists Foundation, Inc., the Sharon & William Bauce Foundation, the Norton B. Gilula Graduate Student Fellowship, David and Ursula Fairchild, the Fletcher-Jones Foundation, and the Louis R. Jabinson Investigatorship Fund for Graduate Education. Their contributions to the Graduate Studies Program supported our commitment to scientific excellence.

Each year, students from the chemistry and MCSC programs invite prominent researchers at the forefront of the biological and chemical sciences to participate in the graduate program's Distinguished Lecturer Series. Speakers who participated in the series this year included Stephen L. Buchwald, Massachusetts Institute of Technology; Chaitan Khosla, Stanford University; Ignacio Tinoco, University of California, Berkeley; Michael Rossmann, Purdue University; Lynne Regan, Yale University; Philip Sharp, Massachusetts Institute of Technology; Joanne Stubbe, Massachusetts Institute of Technology; Samuel I. Stupp, Northwestern University; and John Wood, Yale University.

To address the needs of the community, a highly motivated group of graduate students continue to enhance curriculum for high school science teachers. The enhancements include hands-on experiments that can be used in the classroom and didactic presentations on state-of-the-art research topics and techniques for TSRI's Science Partnership Scholars Program. In addition, several graduate students serve as mentors to high school students through TSRI's Research Education Program, which was created to expose students to a variety of contemporary issues in basic biomedical research, provide hands-on laboratory experience, and motivate and prepare students for continuing education in the sciences.

The graduate program held its annual retreat in September at the Shelter Pointe Hotel and Marina. The objectives of the retreat are to encourage scientific discussion among students and faculty, provide a forum for presentation of a broad range of research topics by students, and serve as a measure of the scientific excellence of graduate students at TSRI. Each of the following students received a $300 academic allowance: Nadim Jessani, for best MCSC poster; Jawdat Al-Bassam, for best MCSC presentation; Songpon Deechongkit, for best chemistry poster; and Federico Bernal, for best chemistry presentation. The event was attended by approximately 175 students and 30 faculty members.

In addition, Ian Wilson, D.Phil., announced the recipient of this year's Jairo H. Arevalo Award: fourth-year chemistry student Fraser Hof. The graduate program established the one-time $3,000 fellowship in memory of Jairo H. Arevalo, TSRI's first recipient of a doctoral degree. The criteria for selection are qualities of academic scholarship, achievement, enthusiasm, motivation, commitment, and thirst for knowledge that were so apparent in Arevalo.

More than 100 TSRI faculty members provide instruction to 78 students in the chemistry program and 73 students in the MCSC program. We are grateful to all of the senior scientific staff for volunteering to provide the leadership and expertise necessary to maintain and enhance this program that serves as a reflection of the institute's standard for scientific excellence. ■

Dear Friends:

The year 2001 has been an eventful one for our institution. At TSRI, a succession of stellar achievements by our scientists was crowned by the award of the Nobel Prize in Chemistry to K. Barry Sharpless, Ph.D., W.M. Keck Foundation Professor of Chemistry, in October.

It is impossible to review the past year without focusing on the events of September 11, and the ensuing days and weeks of national grief, compassion, mutual support and resolve. The Scripps Research Institute Board of Trustees, our staff, scientists and students, are committed to bringing our considerable intellectual and technical capabilities to bear upon emerging national concerns. A number of our scientists are already working with various federal agencies, including the Department of Defense. At the same time, our scientists and their staffs continue their important work to unravel the fundamental mysteries of life, and disease.

The support of our philanthropic community has always been a key element in our ability to rapidly respond to emerging priorities in science and medicine. On the following pages you will see the names of those who have donated support to the Institute in the year 2001 as well as names of those who have informed us that they have named TSRI as a beneficiary in their estate.

A gift of support to TSRI creates a partnership between the donor and the institution which we deeply value. Our young scientists as well as our senior investigators are continually renewed by the ability to rapidly pursue new discoveries. That freedom is made possible in large part by your generosity.

We thank you for your continued support during this critical time.

Sincerely,

Deeda Blair

Deeda Blair
Chair of the Development Committee

The Scripps Research Institute is many things to many people. Scientists in our laboratories are dedicated to discovery research in a number of different programs as well as education and community outreach through science internship programs for teachers and students. The generosity of our donors significantly impacts our ability to pursue new avenues in medical science. On the following pages we recognize those who have been donors during this year. In sidebars, we give special recognition to some of the people and foundations who have shown special interest in specific institutional programs.

Major Donors to the Scripps Research Institute

Special Acknowledgment

The following are those individuals and organizations who, over the years, have given $1 million or more in support of investigations at the Research Institute. We specially honor them and recognize their dedication to the advancement of medical science.

American Cancer Society, Inc.
American Heart Association
David K. Anderson Charitable Lead Trust
Gordon M. Anderson Charitable Lead Trust
Anonymous (15)
Arthritis Foundation
Dr. Arnold O. Beckman and the Arnold and Mabel Beckman Foundation
Becton Dickinson and Company
Cancer Research Institute, Inc.
The Council for Tobacco Research
Mr. and Mrs. Richard A. Cramer
Damon Runyon-Walter Winchell Cancer Fund
Harold L. Dorris Neuroscience Foundation
Helen L. Dorris Foundation
Walter Fitch III
Juanita Francis
Dr. and Mrs. Cecil H. Green
Mr. and Mrs. Ernest W. Hahn
Ernest W. and Jean Hahn Charitable Trust
Lita Annenberg Hazen
Juvenile Diabetes Foundation
W.M. Keck Foundation
Mr. and Mrs. W. Keith Kellogg II
Mr. and Mrs. Eugene V. Klein
Gladys Q. Knapp
Leukemia Society of America
Mr. and Mrs. John D. Lusk
Lucille P. Markey Charitable Trust
G. Harold and Leila Y. Mathers Foundation
Mr. and Mrs. John Jay Moores
National Multiple Sclerosis Society
Pitman Moore, Inc.
The Rockefeller Foundation
Mr. and Mrs. Donald Roon
Mr. and Mrs. Leo Roon
Mr. and Mrs. John Safer
The E.W. Scripps Family
Donald P. and Darlene V. Shiley
Aline W. and L.S. Skaggs
The Skaggs Institute for Research
Mrs. Betty L. Springer
Sam and Rose Stein Charitable Trusts
Buddy Taub Foundation

October 1, 2000 to September 30, 2001

The following list acknowledges the generosity of the many friends of The Scripps Research Institute who contributed during the past year.

$100,000 or more

American Cancer Society, Inc.
American Diabetes Association
American Heart Association
Arthritis Foundation
Donald E. and Delia B. Baxter Foundation
The Arnold and Mabel Beckman Foundation
Oscar A. Bigler
Burroughs Wellcome Company
Cancer Research Institute, Inc.
Mrs. William E. Conner
Damon Runyon-Walter Winchell Cancer Fund
Dr. and Mrs. John D. Diekman
Harold L. Dorris Neuroscience Foundation
Helen L. Dorris Foundation
Ellison Medical Foundation
Mr. and Mrs. George L. Forman
Theodore Hart
Lita Annenberg Hazen Foundation
The Hearst Foundation, Inc.
Howard Hughes Medical Institute
Juvenile Diabetes Foundation
Leukemia Society of America
Lindamood-Bell Learning Processes, Inc.
Mrs. Virginia M. Martin
G. Harold and Leila Y. Mathers Foundation
Merck Genome Research Institute
Mr. and Mrs. John Jay Moores
National Multiple Sclerosis Society
The David A. Packard Foundation
Peninsula Community Foundation
Gustavus and Louise Pfeiffer Foundation
Mr. and Mrs. John Safer
Dr. and Mrs. Paul Schimmel
Thomas L. and Ruth F. Shepherd
The Skaggs Institute for Research

$50,000–$99,999

Anonymous (1)
ARCS Foundation, Inc.
William and Sharon Bauce Family Foundation
CaP CURE
Mrs. Lela W. Cotter
Gretchen M. Dixon
Camille and Henry Dreyfus Foundation

Interface of Biology and Chemistry |

Arnold O. Beckman, Ph.D., one of the giants of 20th century science and technology, realized very early the importance of the interface between biology and chemistry. When TSRI launched an ambitious program to bring biologists and chemists together in a single facility to promote a merging of the sciences, the Arnold and Mabel Beckman Foundation was among the first in support of the program. The result is the Arnold and Mabel Beckman Center for the Chemical Sciences.

Joseph P. Drown Foundation
Mr. James H. Farwell
Fidelity Investment Charitable Gift Fund
Genentech, Inc.
Susan G. Komen Breast Cancer Foundation
March of Dimes Birth Defects Foundation
Mr. Robert E. Martini
National Foundation for Cancer Research
Mr. Robert P. Scripps, Sr.
Torrey Mesa Research Institute
W.E. Walker Foundation

$25,000–$49,999

American Chemical Society
American Parkinson Disease Association
Amgen, Inc.
Anonymous (2)
Mr. Robert E. Bergh
Boehringer Ingelheim Ltd.
The Robert S. and Eloise C. Bowers Foundation
Bristol-Myers Squibb Company
Jane Coffin Childs Memorial Fund
John G. Davies, Esq.
Elizabeth Glaser Pediatric AIDS Foundation
Mr. James E. Iverson
Merck & Company, Inc.
Myasthenia Gravis Foundation Inc.
Rett Syndrome Research Foundation
The San Diego Foundation
Schering Sales Corporation
Syrrx, Inc.
Mr. and Mrs. Hans R. Wiener
Yamanouchi USA Foundation

$10,000–$24,999

Anonymous (1)
Mrs. Betty Anne Money Arenz
Asahi Bank
Mr. George H. Conrades
Cystic Fibrosis Foundation
Cytopia Pty. Ltd.
Anneliese E. Didier
The Ray Thomas Edwards Foundation
Mr. and Mrs. David C. Fairchild
H. Fort Flowers Foundation, Inc.
Mr. and Mrs. Eugene M. Foster
Gencorp Foundation, Inc.
Gilead Sciences
Hereditary Disease Foundation
Huang Foundation
Mr. Shing-Yi Huang
Hutter Family Foundation
Inflazyme Pharmaceuticals Ltd.
Eugene V. Klein
Mrs. Lillian L. Kremer
Sigmund and Beverly L. Laube
Life Science Charitable Foundation
Maurice J. Masserini Charitable Trust
Mellor Family Foundation
Multiple Sclerosis of Canada
Mr. Winnford W. Nance
Otsuka Pharmaceutical Co., Ltd.
Pfizer Inc.
Pharma Design Inc.
Christopher Reeve Paralysis Foundation
The Florence Riford La Jolla Fund
Mrs. Jack T. Sakioka
Sangstat Transplant Company
Scleroderma Foundation
Mrs. Lesly Starr Shelton
Mr. and Mrs. Mace Siegel
Alfred P. Sloan Foundation
Vernalis Research Ltd.
Albert L. Weickert
Wyeth Lederle Japan Ltd.
Carl E. Wynn Foundation

$5,000–$9,999

Agouron Pharmaceuticals Inc.
Anonymous (3)
Marjorie V. Barg
Mr. Paul J. Bowron
Mr. and Mrs. Alfred L. Brosio
Mr. Clarence L. Conzelman
Mr. Glen Daugherty
Mr. and Mrs. James W. Dennis
Mr. and Mrs. Richard A. Erley
Lawrence C. Horowitz, M.D.
Mr. and Mrs. Bud Krause
Mr. Hector V. Leon
Lawrence W. Lytton
Morphochem, AG
Ronald J. Newell
Aneta May Oliver
Mr. and Mrs. Bruce K. Osborne
Philip Morris Companies Inc.
I. Robert and Sylvia Carmel Schlanger Foundation
Mr. William G. Sommerville
The Tappan Foundation
USA Foundation-Wallace
Mr. and Mrs. Robert G. Wallace

$1,000–$4,999

Abbott Laboratories
Gene and Elaine Allen Foundation
Allen Graham Inc.
Anonymous (6)
AT&T Foundation
Jo Ann Badeau
Bank of America Foundation
Bayer Corporation
Baylor College of Medicine
Best Family Foundation
Bill's Trailerland Sales Co.
Mrs. William McCormick Blair, Jr.
Dr. Gunter Blobel
Louis L. Borick Foundation
Ms. Judy Bork

Ms. Jane C. Botello
Mr. and Mrs. H.G. Bouris
Mr. and Mrs. Robert K. Break
La Verne and Blaine Briggs
Buck Family Foundation
Mr. and Mrs. John S. Callahan
Mrs. Raymond E. Cannon
Capital One Services Inc.
Mr. and Mrs. David S. Carton
Thomas E.K. Cerruti
Mr. and Mrs. Andrew Cianciotto
Cliff C. Clark, Jr.
Mr. and Mrs. Shelby Collinsworth
Community Foundation of Silicon Valley
Community Foundation of the United Jewish Federation of San Diego County
James C. Conly, PhD
Mrs. Nancy A. Connell
Mr. Charles R. Cono
Mrs. Van Blackie Cooke
Mr. and Mrs. Moody Covey
Malcolm Cravens Foundation
Mr. and Mrs. Victor M. Cruz
Mrs. Florance G. Cuno
George J. Daou Trust
Mr. and Mrs. Raymond L. deKozan
Mrs. Ralph Dexter
Discovery Partners International, Inc.
Dr. and Mrs. Frank J. Dixon
Mrs. Charles K. Duncan
The Dupont Merck Pharmaceutical Company
Mrs. Richard K. Eckert, Sr.
Mr. and Mrs. Ronald C. Erbetta
Helen Trahan Farschon
James and Louise Farschon
Federation Foundation of Greater Philadelphia
Mr. and Mrs. Willis L. Fehlman
Ms. Joan R. Fisher
Mr. and Mrs. Stanley Fishfader
Mr. and Mrs. Barry C. Fitzpatrick
Mrs. Ward Fitzpatrick
Fluidmaster, Inc.
The Jewell Fox Trust
Robert E. Francis
Mary Jo Frederiksen
Mr. C. Hugh Friedman and Ms. Lynn A. Schenk
Mrs. Lourdes A. Garcia
Mrs. Roger T. Gilmartin
Mrs. Eugenia C. Glow
Mr. and Mrs. Jack Greening
Mr. and Mrs. Arthur V. Grimes
Mr. and Mrs. Robert C. Gunness
Mrs. Betty Scripps Harvey
Mrs. Bruce A. Hecker
Mr. and Mrs. William J. Hefner
Cdr. Harry E. and Dr. Anna P. Helgeson
Mr. and Mrs. Arthur H. Hill
Mr. and Mrs. John P. Howe
Mr. and Mrs. Roger Howe
Mr. Alan R. Hunter
Mrs. Richard P. Irwin
Mr. and Mrs. John J. Jachym
Mr. and Mrs. Oliver B. James, Jr.
Mr. and Mrs. Lloyd L. Johnson
Johnston Family Foundation
Mrs. Richard W. Judd
Mr. and Mrs. William G. Karnes
Mr. and Mrs. Rexford P. Kastner
David B. Katzin, M.D., Ph.D.
Mr. and Mrs. Richard L. Kole
Robert C. Kyle
Mr. and Mrs. W.R. Lake, Jr.
Bess Lambron
Mrs. Cecelia Lance
Mr. Robert Landers
Mrs. Helen S. Levitt
Mr. Leon J. Levitz
Mr. and Mrs. Jackson T. Lewis
Mr. Robert M. Loch
Mr. and Mrs. William Low
Mrs. Ermina S. Makle
Mr. and Mrs. William J. Mason
Mr. and Mrs. Oscar G. Mayer
Professor James O. McCaldin
Edith L. McCullough. Ph.D.
Mr. and Mrs. Owen L. Miller
Mrs. Roy K. Mitsuuchi
Mr. and Mrs. John Mule
Mr. and Mrs. Floyd Nelson, Jr.
Neogenesis Drug Discovery, Inc.
Mr. and Mrs. George K. Nervig
Mr. and Mrs. Winston B. Newell, Jr.
Mr. and Mrs. David Oliver
Dr. and Mrs. Stanley J. Pappelbaum
PARAID
Mr. and Mrs. Robert G. Park
Joseph J. Pertusati
Pharmacia & Upjohn Co.
Ms. Mildred Pilot
The Ponagansett Foundation, Inc.
Mr. and Mrs. Thomas J. Pope
Price Charities
Mrs. Edna F. Pulver
Edward W. Rawlins, Jr.
Mrs. George E. Richardson
Philip R. Ricker
Ms. C. Kitty Rodman
Paul G. Rogers, Esq.
Mrs. Louis Roripaugh
Mr. and Mrs. Angelo J. Rossi
The San Diego Foundation
San Diego Padres Baseball Club
Mr. and Mrs. Yoshiya Sanbonmatsu
Sara Lee Foundation Matching Gift Program
Mrs. Helen E. Saville
Iris M. Schleibaum
Mr. and Mrs. Sherwood Schwartz
Mr. and Mrs. Charles E. Scripps, Sr.
Sempra Energy
Senturia Family Fund

Interface of Biology and Chemistry |

L. Sam and Aline W. Skaggs recognized the importance and promise of this convergence of disciplines, and provided funding for laboratories in the Beckman building. Then, to carry the momentum even further, Mr. and Mrs. Skaggs created and funded an entirely new Institute, the Skaggs Institute for Chemistry and Biology. The level of support provided to TSRI by Mr. and Mrs. Skaggs is unparalleled by any other gift.

Other New Initiatives | John and Becky Moores's generous gift in 1998 launched the creation of a new endeavor, the Institute for Childhood and Neglected Diseases, which was dedicated in October of 2001. Among the newly recruited investigators to the Institute are scientists studying autism and malaria, among several other disciplines.

Mr. and Mrs. Robert B. Shea
William H. and Barbara A. Short
Mr. and Mrs. Richard F. Silva
Captain Harriet A. Simmons
Mrs. John T. Snite
Ms. Mary C. Soares
Mr. Michel H. Solari
Robert and Carole Sopko
Mr. Norman J. Sugg
Mr. and Mrs. Charles E. Suhr
Sundstrand Power Systems
Mrs. Clarence L. Swan
Ray and Shirley Tritten
Valley Trust Deed Services, Inc.
Vancouver Lions Club
Jim and Linda Walker
Mrs. Clara S. Weerts
Mr. and Mrs. Robert C. Weiss
Mr. and Mrs. Earl D. Williams
Wood-Rill Foundation
Wyeth Ayerst Laboratories
Ms. Lauren Yaffe and Ms. Sidney Huang
Penny S. Zorn

$1–$999

Mr. James G. Abraham
Mr. George H. Adams, Jr.
AJC Enterprises
Mr. and Mrs. Vito J. Altieri
Anadys Pharmaceuticals
Anonymous (7)
Antiquorum
Mr. Martin M. Astl
Dr. and Mrs. Sven A. Bach
Ms. Judi Bailey
Mrs. Jack Baker
Mr. and Mrs. Bert Ball
Mrs. Charles F. Bannan
Mrs. Ross Barber
Mr. and Mrs. Robert L. Bardini
Mr. Franklin P. Barnhill
Mrs. Freda F. Bazley
Mr. and Mrs. John E. Beal
Mr. and Mrs. Donald A. Beanston
Ms. Anne Bearman
Mr. and Mrs. B.D. Bennett
Mr. and Mrs. Vincent E. Benstead
Ms. Naomi M. Bergmann
Mr. and Mrs. Phillip S. Bettoli
Mr. Daniel H. Bindler
Mr. and Mrs. Stanley E. Birstein
Mr. and Mrs. Marshall V. Bittick, Jr.
Mrs. Laura F. Bjorseth
Mr. and Mrs. Ed Blitz
Mr. Theodore Blumenstock
Mr. Samuel Boodman
Mrs. Richard N. Bowker
Mr. and Mrs. Charles C. Bowles
Mr. and Mrs. Harry A. Bowman
Mr. Steven Bramson
Mr. and Mrs. Tom Bronkow
Mr. and Mrs. John W. Brown
Ms. Bonnie Brownell
Mr. Matthew Brush
Mrs. Barbara A. Burklow
Ms. Ethel C. Burress
Mr. and Mrs. Norman E. Byrum
Mr. and Mrs. John S. Callahan
Mr. and Mrs. Glendon M. Campbell
Canterbury Capital Services, Inc.
Mr. and Mrs. Donald F. Capp
Mr. and Mrs. Marvin Carls
Major and Mrs. Manuel L. Carrasco
Mr. and Mrs. William F. Carroll
Mr. and Mrs. David S. Carton
Mr. and Mrs. F.P. Castaneda
Ms. Connie G. Chaney
Chevron Products Company
Mr. Nam-Hai Chua
Rear Admiral Steve S. Clarey
Mr. and Mrs. Harvey R. Clark
Ms. Joann P. Clark
Mr. Michael Clover
Mr. and Mrs. Rodney L. Cook
Mr. and Mrs. M. Lee Cotterman
Mr. Paul H. Cour
Ms. Lois P. Criswell
Mr. Samuel R. Crookshanks
Cubic Corporation
Clifford D. Cummins, M.D.
Ms. Louise E. Cunningham
Mr. and Mrs. Samuel Y. Dale
Mrs. Robert Day
Mrs. Carlos David de Malamud
Ms. Maria Luisa A. de Rodriguez
Mr. and Mrs. Charles W. Dealy, Jr.
Mr. John J. Delibos and Ms. Irene E. Delibos
Ms. Mary Lou Denison
Mr. and Mrs. Karl A. Dennis
Mr. John J. Di Giovanni
Mr. and Mrs. Joseph L. Dondero
Mr. and Mrs. Richard Dondero
Mr. and Mrs. Edward W. Drcar
Ms. Charlotte B. Dreiman
Ms. Shirley Dreiman
Mrs. Betty A. Duffy
Mr. and Mrs. Dale W. Duncan
Mr. and Mrs. Sewell N. Dunton, Jr.
Mr. Richard W. Dutton and Mrs. Susan L. Swain
Mrs. Shirley P. Edwards
Ms. Beverly E. Ellis
Esskay Properties
Mrs. Earl R. Evans
Mr. Thomas D. Evans
Mr. and Mrs. John E. Evenson
Mr. and Mrs. Robert Falkenstein
Ms. Sunni Lynn Farkas
Ms. Geraldine E. Faucett
Mrs. Walter Feathers
Mr. and Mrs. Robert A. Ferguson
Ms. Martha L. Ferris
Ms. Phyllis Firtel
Mr. Harold A. Fisher
Mr. and Mrs. John S. Fisher
Mrs. Dorothy F. Flesch
Mrs. Emi M. Fors
Mr. and Mrs. M. Gordon Forsyth

Mr. Leonard J. Frankel
Mr. and Mrs. George J. Franzen
Ms. Bettie L. Furuta
Mr. and Mrs. Armando Gallego-Moreno
Ms. Ruth Gans
Mr. and Mrs. Salvador M. Garay
Mr. Raoul S. Gazi
Mr. and Mrs. Ivan A. Getting
Mr. David P. Giesing
Mr. Ray Gillcrest
Mrs. Judith Gillease
Mr. Morris A. Glantz
Mr. Clarence R. Graham, Jr.
Mr. Kevin P. Grant
Mrs. Ruth G. Graul
Dr. Oscar Greene
Mr. and Mrs. William R. Griffith, Sr.
Mr. Irwin Grossman
Mr. and Mrs. Jesus Gutierrez
Mr. Rolf Haas
Mr. Jeffrey Hachlowski and
Ms. Diane Baker
Dr. and Mrs. Harold R. Hall
Mr. Elmo L. Halladay
Ms. Susan T. Hamamoto
Ms. Rita M. Hanf
Ms. Ann Harelson
Dr. and Mrs. Seymour A. Hartman
Mr. Carl J. Hattermann
Mr. and Mrs. Robert I. Heisner
Ms. Jeannie P. Hibner
Hines Interests Limited Partnership
Mr. James Hirschfield
Mr. Theodore R. Hobson
Mr. and Mrs. Frank W. Hoehn
Mr. and Mrs. Ronald P. Hoffman
The Hollander Foundation
Ms. Nancy S. Hongola
Dr. and Mrs. Paul W. Horne
Mr. and Mrs. Morris E. Horsley
Mr. and Mrs. Lee Houseman
Belle Huang, M.D.
Mr. and Mrs. Richard I. Humphreys
IBM International Foundation
Mr. Jerome B. Ingber
Mr. and Mrs. John C. Ingram
Mr. and Mrs. David L. Isa
J.J.K. Consulting Services
Mr. and Mrs. Robert A. Jacobson
Mr. Abraham Janoff
Mr. and Mrs. Bill R. Jones
Ms. Grace V. Jorgensen
Mr. and Mrs. Edward S. Juchniewicz
Mr. and Mrs. Gene Judd
Mrs. Frances R. Kahan
Ms. Virginia P. Kantor
Mr. Philip G. Kaplan
Ms. Kay Ann Kelly
Mr. and Mrs. Albert D. Kern
Mr. Monroe W. Kirkman
Dr. Marc W. Kirschner
Ms. Donna L. Kisela
Mr. and Mrs. Buster I. Kiyono
Mr. Jerry Klein
Kline Family Foundation
Mrs. Marie L. Kline
Mr. Stephen M. Koltai
Dr. and Mrs. Samuel Krain
Mr. and Mrs. Mitchell E. Kronenberg
Mr. and Mrs. Richard G. Kuck
Mr. and Mrs. David S. Lacey
Mr. and Mrs. Walter G. Lake
Mr. and Mrs. Robert C. Larson
The Learning Tree
Mr. Charles P. LeBeau
Ms. Mary Lee Ledbetter
Mr. and Mrs. Charles W. Lehner
Mr. and Mrs. Herb Lemelle
Mr. and Mrs. Charles LeMenager
Ms. Carey S. Leva
Mr. and Mrs. Harold C. Levy
Mr. and Mrs. Gene Littler
The Loan Factory, Inc.
Mr. and Mrs. Donald J. MacDonald
Mr. William R. Machgan
Mr. and Mrs. Calvin C. Mank
Ms. Daisy Martin
Ms. Sandi Mataga
Mr. Frederick K. McCann
Mr. and Mrs. Richard E. McCants
Mr. and Mrs. Don L. McCarty
Mr. James D. McCoy
Ms. Sally D. McDonald
Mr. J. Richard McIntosh
Ms. Margaret F. McIrvin
Ms. Pam McKenna
Mr. and Mrs. Michael McKinzie
General and Mrs. Kenneth McLennan
Ms. Diana L. McNeil
Mr. Donald E. McRoberts
Mr. and Mrs. John W. McRoskey
Mr. Job F. Measom
Messner & Smith
Mr. and Mrs. Kenneth J. Metzgar
Mr. and Mrs. Barth A. Mikals
Mr. Newell L. Miller
Mr. and Mrs. Walter W. Mitchell
Mr. and Mrs. Lajosh Mohachy
Mr. Frank Anthony Mongulla
Mr. and Mrs. Neil Morgan
Ms. Kathryn A. Morrow and
Mr. Lenard Nissenson
Mrs. Leonie Moses
Drs. R.S. and Barbara Mullen
Mr. and Mrs. Vincent R. Munar
Colonel and Mrs. Edward S. Murphy
Mr. Thomas L. Mushegain
Mr. and Mrs. James E. Musselman
Mr. and Mrs. John F. Nastrini
Mr. and Mrs. Gregory Nelson
Mr. Harry M. Nickel
Mr. and Mrs. Phillip D. Nico
Ms. Ingrid R. Niesman
Northern Trust Investments, Inc.
Mr. George K. Ojakian
Mr. Edward J. O'Rourke, Sr.
Dr. and Mrs. Martin E. Orro
Mr. Charles Osborn

Other New Initiatives | Helen L. Dorris's advocacy for mental health once again has inspired her to launch a new initiative at TSRI for the study of neurological and psychiatric disorders of children and adolescents. Housed with the Institute for Childhood and Neglected Diseases, this new example of her generosity will be directed by Dr. Benjamin Cravatt.

Graduate Program | ARCS Foundation

(Achievement Rewards for College Scientists) approved TSRI's graduate program for inclusion in their awards program in 1997. Since that time, the ARCS Foundation has supported the graduate program generously, awarding a total of nine scholarships and fellowships in each of the last three years. ARCS is known for its support of only the most prestigious graduate programs, and TSRI is proud to be a member of the supported institutions.

Jo Anne Overleese, M.D.
Mr. Harold I. Palash
Mr. and Mrs. Barton M. Palmer
Paoluccio, Paoluccio Associates
Ms. Genevieve Pawlowski
Mr. William R. Payden
Mr. and Mrs. D.B. Pehrson
Dr. Camillo Peracchia
Mr. Marvin Perlman
Mr. Thomas B. Phillips, Jr.
Mr. and Mrs. Nicholas Platis
Mr. A.E. Pratt
Mrs. George Price
Professional Counseling
The Quaker Oats Foundation
Dr. James P. Quigley
R&J Dondero, Inc.
Mr. and Mrs. Russell J. Ramsland
Mr. Lawrence L. Reibman
Ms. Annie E. Reynolds
Mrs. Ida M. Ricci
Mr. and Mrs. John Rider
Mr. and Mrs. Darren J. Robbins
Mrs. Esthere Roberts
Mr. Vird A. Roberts
Mr. and Mrs. Gary L. Rold
Dr. and Mrs. Abraham Romanowsky
Captain A.K. Romberg, USN (Ret.)
Mr. and Mrs. Herman H. Rosenfeld
Mr. and Mrs. Floyd R. Ross
Captain Richard B. Ross and Mr. Keith E. Ross
Mr. and Mrs. John W. Rowe
Ms. Evelyn O. Roy
Dr. and Mrs. Milton A. Rubin
Mrs. Mildred C. Saal
David A. Sabourin, D.D.S.
Mrs. Fae P. Sanger
James J. Santiago Enterprises, Inc.
Mr. Peter Satir
Mr. and Mrs. Robert G. Schaffeld
Mr. Stuart Scheidler
Ms. Marian M. Schemmer
Mr. and Mrs. Edmund W. Schloss
Mrs. Vesta Jenks Schmidt
Dr. and Mrs. James A. Schoenberger
Mr. and Mrs. George Schuller
Ms. Pamela Schulte
Mr. and Mrs. Robert E. Schulz
Ms. Naomi Schwartz
SDG&E Employees Contribution Club
Mr. and Mrs. Carl W. Sedler
John R. Seffrin, Ph.D.
Mr. James Roy Seitz, Jr.
Mr. and Mrs. James R. Shaffer
Admiral and Mrs. U.S. Grant Sharp
Mrs. Lee C. Shaw, Sr.
Mr. and Mrs. Michael Sherman
Mr. Edmund J. Shoop
Mr. and Mrs. Bertram N. Shure
Mr. and Mrs. William H. Sievers
Mr. Peter Sih
Mrs. Freda Silver
Dr. and Mrs. Samuel C. Silverstein
Ms. Eugenia Simpson
Mrs. Frieda B. Singer
Dr. and Mrs. Charles G. Smith
Mr. George Smalley
Mr. and Mrs. Robert W. Smothers
Mr. and Mrs. Charles E. Snyder, Sr.
Ms. Betty L. Southard
Mrs. Seema Sperling
Mr. and Mrs. Warren Reed Sprinkel
Mr. Andrew H. Stallings
Ms. Greta L. Stancik
Dr. and Mrs. J. Newell Stannard
Ms. Kathryn M. Starr
Diane Stein Memorial Fund
Mr. and Mrs. Michael G. Stein
Dr. and Mrs. Donald A. Stewart
Jack and Mark Stiefel Dairy
Mr. and Mrs. Horst H. Streblow
Mr. Richard K. Strowmatt
Mr. and Mrs. William L. Stugart, Jr.
Ms. Ann E. Summers
Mrs. Charles Alva Swanburg
Mr. Earl H. Swanson
Mr. and Mrs. Arthur N. Talbot
Mr. and Mrs. Douglas E. Talmon
Mr. Bernard Tardif
Mr. and Mrs. Benjamin G. Thomas
Mr. and Mrs. Billy J. Thomas
Mr. Samuel L. Travis
Mrs. Helen E. Trethaway
Ms. Marian C. Trollan
Roger Tubbesing, D.D.S., and Barbara Tubbesing, Ph.D.
Mr. and Mrs. Richard A. Tuthill
Twentieth Century Fox
Mr. and Mrs. Gerard Tynen
Mr. Stephen A. Ugolini
Valley Trust Deed Services, Inc.
Mrs. Angelina G. Velasco
Mr. and Mrs. Frank A. Verstuyft
Mr. and Mrs. Alvaro R. Virissimo
Ms. Margaret H. Vlcek
Mr. and Mrs. Jerry Wahl, Sr.
Mr. T.M. Walker
Mr. and Mrs. Donald R. Watkins
Dr. and Mrs. Ansel Watrous
Mr. Matthew Watson
Mrs. Edith B. Watts
Mr. and Mrs. Arthur Weiner
Mrs. Patricia R. Welsh
Mr. and Mrs. H.F. Westphal
Mr. and Mrs. Joseph Wiener
Mr. Robin L. Williams
Mr. Roy E. Williamson
Mr. Leonard Willig
Mr. John H. Wilson
Mr. and Mrs. Kenneth A. Wolski
Ms. Charmaine K. Woolley
Mr. and Mrs. Ching-Sing Yang
Mr. Gerald Yavitz

Ms. Lisa Yorhis
Mr. and Mrs. Robert W. Young
Mr. Gerald J. Zafft
Mr. and Mrs. William Zarkades

Faculty and Staff

Jo Ann Anderson
Dr. Bernard M. Babior
Dr. Ernest Beutler
Dr. Gary M. Bokoch
Michael J. Buchmeier, Ph.D.
Dennis R. Burton, Ph.D.
Edward K. Chan, Ph.D.
Hanna Damke, Ph.D.
Gregory J. del Zoppo, M.D.
Dr. Thomas S. Edgington
M.G. Finn, Ph.D.
Dr. Nicholas Gascoigne
Elizabeth D. Getzoff, Ph.D.
Dr. M. Reza Ghadiri
Robin B. Goldsmith
Dr. Joel Melvin Gottesfeld
Luca Guidotti, Ph.D., D.V.M.
Wendy Lynn Havran, Ph.D.
Dr. Mary Jo Heeb
Steven J. Henriksen, Ph.D.
Dr. Paul G. Heyworth
James A. Hoch, Ph.D.

Graduate Program | **The William and Sharon Bauce Family Foundation has supported three graduate students each year since 1997. Two of the students supported by the Bauce Fellowship have been awarded the Ph.D., and a third is in his final year of study. Two new students were selected this year as recipients of the fellowships. This continuing support by Bill and Sharon Bauce is a testament to their lasting commitment to excellence and advancement of medical research, and to supporting the education and training of tomorrow's scientists.**

Dr. Kim D. Janda
Dr. Jeffery W. Kelly
Mr. Tony Kerr
Dr. Ulla G. Knaus
George F. Koob, Ph.D.
Mr. Arnold LaGuardia and
Mrs. Susan Mazza
Richard A. Lerner, M.D.
Mark R. Mayford, Ph.D.
Dr. David Nemazee
Dr. and Mrs. K.C. Nicolaou
Dr. Michael B.A. Oldstone
Dr. Arthur J. Olson
Dr. Anthony J. Pelletier
Kenneth Michael Pollard, Ph.D.
Vito Quaranta, M.D.
James P. Quigley, Ph.D.
Dr. and Mrs. Wolfram Ruf
Dr. Zaverio M. Ruggeri
Mr. Paul Russell
Dr. Daniel R. Salomon
Dr. Michael F. Sanner
Denise M. Scalzo
Dr. and Mrs. Paul Schimmel
Sandra L. Schmid, Ph.D.
Dr. Gary Siuzdak
Ray Stevens, Ph.D.
John A. Tainer, Ph.D.
Dr. Eng M. Tan
Dr. and Mrs. Peter Tobias
Bruce E. Torbett, Ph.D.
Richard J. Ulevitch, Ph.D.
Peter K. Vogt, Ph.D.
Clare M. Waterman-Storer, Ph.D.
Dr. and Mrs. William O. Weigle
Friedbert Weiss, Ph.D.
Paul Wentworth, Ph.D.
Donna J. Weston
Dr. James R. Williamson
Dr. Curtis B. Wilson
Dr. Ian A. Wilson
Dr. Chi-Huey Wong
Peter E. Wright, Ph.D.
Kaye I. Wynne

Scripps Heritage Circle

Scripps Heritage Circle honors those who have arranged for future philanthropic support of a Scripps institution through a deferred gift. Membership signifies that one has named The Scripps Research Institute or a Scripps Health entity as a beneficiary of a life income trust, a bequest, a gift annuity, a life insurance policy, a life estate or other form of deferred gift. Members of the Scripps Heritage Circle receive The Scripps Heritage, a quarterly financial newsletter, and invitations to the annual Heritage Circle dinner and other VIP functions, as well as invitations to Scripps Presidents' Council events.

If you have arranged for a deferred gift benefiting The Scripps Research Institute and have not yet notified us of your planned gift, please contact our Development Office at (858) 784-9365.

Captain and Mrs. James F. Agnew
Mrs. Shirley J. Ahrens
John Aliotta
Audrie T. Allen
Ms. Helen Alter
Mr. and Mrs. Milo Altman
John R. and Eileen Anderson IV
Gordon and Rita Archibald
Captain Edward S. Arentzen, USN (Ret.)
Mrs. Joseph Aron
Jose C. Bach
Mr. and Mrs. Kenneth G. Bacheller
Mrs. Elaine S. Barber
Mr. and Mrs. Michael D. Bardin
Andrew Barna
Bruce G. Barnes
Dolores Baron
Mrs. Edith Barton
Mr. John Baur
Mrs. Bette J. Becker
Mr. and Mrs. Warren Becker
Dr. Arnold O. Beckman

Graduate Program | The Fletcher Jones Foundation awarded an endowment grant to TSRI in 1994 for ongoing support of a graduate scholar. This generous endowment has provided for initial support of a deserving student each year in the initial years of their graduate studies, thus serving to launch a growing number of promising careers. Permanent endowment such as this is an essential resource to the institution and the graduate program, and a model of support that we seek to replicate many times over.

Mrs. Alan Beerbower
William H. and Ruth Lynn Beers
Mr. Arthur R. Bell
Mr. and Mrs. Leonard E. Bellinson
Mr. and Mrs. Vincent E. Benstead
Mrs. Marjorie Benvenuto
Mrs. Elisabeth Bergan
Mr. Robert E. Bergh
William and Helen Bergmann
Mr. and Mrs. Harold J. Berns
Mr. Douglas F. Bishop
Mr. and Mrs. Lauren W. Blagg
Drs. Gary and Barbara Blake
Don and Thelma Blanche
Dr. and Mrs. Duane E. Blickenstaff
Mr. and Mrs. Richard L. Bloy
Gerald K. Bodamer, D.D.S.
John and Billie Bowen
James Lewis Bowers, Ph.D.
Jeanne G. Brady
Dr. Charles F. Brass
Miss Kathleen Amy Briggs
Mitchell J. and Merle E. Brodie
Mrs. Alfred Brosio
Dr. and Mrs. Robert P. Brouillard
David and Maggie Brown
Ethel B. Brown
Mr. and Mrs. Gregory H. Brown
John W. and Mary D. Brown
Mr. and Mrs. Richard H. Brown
Mr. and Mrs. Richard A. Buckby, Jr.
Mr. and Mrs. Gerard J. Buckley
Mr. and Mrs. A. A. Burnand III
Kathleen M. Burns, R.N.
Anita M. Burr
Mrs. Mary E. Burson
Dr. and Mrs. Donald J. Buser
Mr. and Mrs. Martin B. Buser
Mrs. Frank P. Butler
Dr. and Mrs. Charles A. Camarata
Mr. and Mrs. A. Bruce Campbell
Dr. and Mrs. Charles G. Campbell
Ms. Christine Camus and Ms. Dottie Camus
Edna M. Canham
Jean C. Carrus
Dr. and Mrs. John C. Carson
Mrs. Laine Carter
David S. and Pamela M. Carton
Mrs. Grace Caton
Richard and Gail Cervantez
Dr. and Mrs. John K. Cherry
Mr. Doc Chew
Dolores Childers
Sr. Carol Ann Clark
J. Dallas Clark
Jack and Carol Clark
Madeline E. Clark
Anna D. Cleaver
Alvin R. Coe
Mr. Arthur J. Cohrs
Sidney C. Cole
Marcia Edelman Lemmon Collins
James C. Conly, Ph.D.
Gertrude B. Copeland
Stanley Corbin
Mr. and Mrs. John F. Cota
Mrs. Lela W. Cotter
Mrs. Beverly J. Cramb
Thomas and Barbara Crane
Mrs. Sam Crivello
Mrs. Joseph A. Cuddihy
Mr. Matt Dalton
Mabel I. Danenberg
Mr. Edwin H. Danenhauer
Mr. and Mrs. Geoffrey B. Daniels
Mr. and Mrs. Everett Davis III
Howard D. and Luella M. Davis
Mr. and Mrs. Albert W. Day
James E. and Florence S. De Lano
Mr. and Mrs. Norbert Dean
Mr. Edwin J. Deckelman
John J. Delibos
Mrs. Burgess Dempster
Mrs. Antony Di Gesu
Col. and Mrs. Alvin W. Dill
Raoul M. Dixon
Mr. Robert L. Donley
Ms. Dolores F. Dorsey
Mr. and Mrs. Roy P. Drachman
Mr. and Mrs. G. Wallace Driver, Jr.
Mr. and Mrs. John L. DuBois, Jr.
Sharon and C. A. (Skeets) Dunn, Jr.
Mr. and Mrs. Henri Durand
Mr. and Mrs. Ames S. Early
Dorothy E. Eckert
Mrs. Mildred Lucille Edis
Shirley Joan Ehrlich
Mr. and Mrs. Arnold B. Elkind
Kathryn R. Ellig
Mr. Gates S. Etter
Mr. Clifford Evans
Mr. and Mrs. James W. Evans
Helen Trahan Farschon
Mr. James W. Farschon
Dr. and Mrs. Ralph C. Faucett
Mr. and Mrs. Winfield N. Felker
Mrs. Russell Q. Fellows
Mr. and Mrs. William E. Ferguson
Arline Findorff
Mrs. Robert J. Finnie
Alvin Fishman
Mr. Walter Fitch III
Mr. and Mrs. Edwin J. Fix
Mr. John Fonseca
Dr. and Mrs. Richard G. Fosburg
Alan B. and Cristina Foster
Mrs. Constance T. Fraleigh
Mr. and Mrs. Victor Freudenberger
Mr. and Mrs. Robert B. Fromm
Dr. and Mrs. Allan D. Gale
Mrs. John J. Gartland, Jr.

Dona J. Gastaldo
Mrs. Audrey Geisel
Lynn Genser
Mr. and Mrs. Lawrence W. Gentry
Mr. and Mrs. Sol Gerber
Dr. and Mrs. Nelson Gidcumb
Ms. Doris M. Giegerich
Allan R. Gilbert
Mrs. Gail Stoorza-Gill
Ms. Pauline A. Gillen
Stanley H. Gist
Mrs. Rita R. S. Gittes
Eugenia Cooney Glow
Mrs. Maxwell H. Gluck
Douglas and Sarann Goad
Dr. Leon Goldman
Marie C. and John E. Goode
Howard Leslie Gosch
Peggy Ann Gowan
William A. and Ruth G. Graul
Dr. and Mrs. Peter A. Gray
Matthew E. Greco
Dr. Cecil H. Green
Nathan and Rose Greene
Mr. Vince K. Greiner
Mr. and Mrs. Bruce Robert Grendell
Harry J. and Janice Griffiths
Mr. Herman Gronauer
Mr. and Mrs. Robert C. Gunness
Helen Guyan
Mr. and Mrs. Fred Haag
Mrs. Ardelle B. Haas
Edward and Gene Haddon
Dr. and Mrs. Richard L. Hall
Nancy P. Hallenbeck
Mr. and Mrs. Norman A. Halus
Miss Sally M. Hammes
Mrs. Joseph I. Hammond
Mr. and Mrs. John L. Hanes
Mrs. John Harmeling
Eugene and Florence Harper
Hugh M. and Angeline Harris
Mrs. Tina Lyle Harrower
Dr. and Mrs. Lawrence V. Hastings
Mrs. Susan Stone Hayes
Mrs. Norman J. Nachreiner
Mrs. John M. V. Heldack
Miss Anne Henkin
Mr. Thomas A. Henry, Jr.
Mr. and Mrs. James Herbert
Mr. and Mrs. George Fredric Herrmann
Mr. and Mrs. Gerald D. Heveron
Dr. and Mrs. Steven L. Higgins
Mary J. Hild
Arthur H. and Julie Hill
Mrs. Leslie C. Hill
Mrs. Kenneth E. Hill
Jim L. and Genevieve Hilliard
Mrs. William Hillyer
Drs. David W. Hodgens & Linda K. Olson
Mr. Jerry Hollander
Mrs. Edward D. Holmes
Lavinia E. Holmquist
Mr. and Mrs. Neal Hooberman
Dr. and Mrs. G. Bruce Hopkins
Mr. and Mrs. John Kent Howerton
James Edward Hoyle and Doris M. Hoyle
Dr. and Mrs. E. Woodrow Hunt, Jr.
Ragna Hunter
Mr. Leonard Huntress
Arnold H. E. Hutchinson
Mrs. Gladis B. Innerst
Maureen Ivey
Dr. and Mrs. Sanford M. Izner
Albert Jason
Charles L. Jensen
Mr. Joseph E. Jessop, Jr.
Dr. and Mrs. Eugene A. Johnson
Mr. and Mrs. Harold D. Johnson
Okey B. Johnson, Jr.
Virginia Kahse
Charmaine and Maurice Kaplan
Mrs. William G. Karnes
Mr. and Mrs. Marion S. Karrh
Mr. and Mrs. Henry H. Katz
Mr. and Mrs. Julian Kaufman
Mrs. Robert M. Keane
Mr. and Mrs. W. Keith Kellogg II
Ms. Shirley C. Kemphaus
Lawrence R. and Janet Kempton
Mr. and Mrs. Robert Kerney
Dr. William B. and Marjorie A. Kessler
Richard E. and Bettylou H. King
Mr. John Kipp
Joyce A. Kissane
Mrs. Eugene V. Klein
Mr. and Mrs. W. H. Klure
Mrs. William A. Knoke
Mr. Dirk C. Kok, Jr.
Mrs. Lorraine B. Kratzer
Lillian L. Kremer
Mr. and Mrs. Walter Kurilchyk
Willett R. Lake, Jr.
Mrs. Margaret E. Lange
Norman and Margaret Lassey
Lee and Toni Leichtag
Elizabeth B. Lemenager
Stephen L. and Sophia B. Levy
Ms. Muriel J. Lewis
Mr. Laurie Liddle
Mr. William G. Lignante and
Mrs. Alma F. Giroux-Lignante
Mrs. J T Lipe
Bette Lipsitz
Mr. and Mrs. Jim Long

Graduate Program | Lesly Starr Shelton is a far-sighted philanthropist who has created, through bequests, the future Henry and Rose Starr Scholarship in the Graduate Program of Chemistry, the Turner B. and Lesly Starr Shelton Endowment for Postdoctoral Studies in the field of Chemistry, and an Annual Award for Excellence in Chemistry Graduate Studies in the name of Turner B. and Lesly Starr Shelton. In this way, Lesly has created a lasting memorial to her parents, her late husband, and herself. But most importantly, she has created scholarship support for students at each level of study and training; a gift that will support generations of scholars and scientists in perpetuity.

Summer High School Internship and Teacher Scholars | Chairman of TSRI Board of Trustees John Diekman, Ph.D., and his wife Susan have endowed a summer fellowship for science teachers, which will provide an opportunity for high school and middle school teachers to learn modern laboratory techniques. This is an important component of TSRI's community outreach program for improving levels of science teaching in local schools. This leadership gift demonstrates both the Diekman's dedication and commitment to science at TSRI and to our community.

Mr. Frank LoVecchio
Burl H. Mackenzie
Harriet Maclean
Mrs. William L. MacNeill
Mrs. John D. Macpherson
Mr. and Mrs. Sol A. Maksik
Walter and Eleanor Malen
Jack and Jeanette Malin
Mrs. Edward A. Malmberg
Art and Sandy Mandell
Dr. Howard and Lottie Marcus
Thelma Margolies
Bill and Millie Marshall
Dr. and Mrs. Stuart C. Marshall
Mary C. Mason
Dr. and Mrs. Kenneth P. Mathews
Kyoko Matsuda
Mrs. John McAdams
Lois McAtee
Mrs. Judy McComic
Dr. and Mrs. James McCord
Mr. Charles O. McWhorter
Mr. and Mrs. John C. Merrill
Mrs. Franny B. Mervis
Burton Meyers
Kenneth W. Miller
Dr. and Mrs. James R. Moitoza
Col. and Mrs. Harry F. Mooney
Alvin J. Moore
Mrs. Carleton G. Morehouse
Mr. Robert J. E. Morin
Mr. and Mrs. James E. Morris
Mrs. Carlo A. Mosca
Mr. and Mrs. John Mule
Mr. and Mrs. George A. Murray
Mrs. Harry Nachman
Mrs. Gaines H. Neale
Mr. and Mrs. Nelson Puett
Joan E. Nelson
Mr. and Mrs. Paul E. Nenner
M. J. and June Nestrud
Ronald Newell
Mr. and Mrs. Thomas P. Nickell, Jr.
Mr. and Mrs. David Nightingale
Mrs. Vivian Nordeen
Mr. Edwin W. Nystrom
Mr. and Mrs. Patrick O'Farrell
Mrs. Gordon Oliver
Ms. Germaine T. Olmsted
Mr. and Mrs. Joseph Opperman
Mr. Jere G. Oren
Mr. Robert Ortega
Mr. and Mrs. John D. Orvis
Ms. Lillian Owens
Mr. and Mrs. Walter W. Pabst
Terry Kim Paik, DVM
Dr. and Mrs. H. Vernon Palmer
Mr. Jose Palomo
Ms. Helen Pateman
Mr. Arloe W. Paul
Mr. and Mrs. Phil Paulson
Mrs. Mary B. Peccolo
Dr. Werner P. Pelz
Mr. and Mrs. John M. Pendleton
Jean E. Pepper
Delores Petricevich
Jack P. Pflock, DVM
Reno and Claudia Pierotti
Mr. Carl E. Podlasky
Mr. and Mrs. Leonard Polster
Mrs. HM Poole, Jr.
James R. Pratley
Mrs. Donna K. Prendergast
Dr. and Mrs. Sterling F. Price
Dr. and Mrs. Ernest E. Pund, Jr.
Mr. and Mrs. John L. Quayle
Mary Ann Quinn
Sara A. Raddatz
Mrs. Thelma D. Rankin
Kitty Razook
Mrs. Charles S. Reed
Wendy Patterson Reinan
Miss Jean L. Reinhardt
Mr. and Mrs. Carl W. Reinhart
Lela Rettig
Mr. and Mrs. Trumbull Richard
Mr. and Mrs. James K. Richardson
Mrs. Phyllis Richman
Don L. and Georgia I. Richter
Mr. Kevin J. Rigsbee
Ms. Lori L. Rigsbee
Dr. and Mrs. Donald J. Ritt
Mr. Arthur Robbins
Dr. and Mrs. Norman C. Roberts
Dr. and Mrs. John P. Roffinella
Donald and Sarah Rogers
Mr. and Mrs. Donald Roon
Ruth and Herman Rosenberg
Dorothy Beidler Runyan
Mr. and Mrs. Richard E. Ryan
Mrs. Helen E. Sachs
Mrs. Sy Salkowitz
Mr. Herbert Sallar
Dr. James H. Sands

Summer High School Internship and Teacher Scholars | The William Randolph Hearst Foundation has provided an endowment that will support up to four summer high school interns in the TSRI Science Outreach Program. This is a vitally important gift that will help to assure the continuation of this very successful program, one that stimulates and nourishes the young minds that will become the scientists of the future.

Mrs. Ernest Schieber
Hans and Muriel Schiff
Estelle Schiller
Alfred F. Schmitt
Ben V. Schneider
Ms. Deborah E. Schoeny
Benjamin D. Schulman
Dr. and Mrs. Louis J. Schwartz
Grover Schwarzauer
Mr. and Mrs. Charles R. Scott
Mr. and Mrs. Harry H. Sealy
Edith Seidel
Mrs. Wilda Jones Shafer
Lesly Starr Shelton
Bill N. Shepard, M.D.
Dr. and Mrs. Harold H. Shively, Jr.
William and Barbara Short
Barbara Siniscalchi
Mr. and Mrs. Lawrence K. Sinz
Susan J. Skolnik
Mr. and Mrs. Bradford Smith
Mrs. Fern Campeau Smith
Mr. Orison Smith
Mr. Walton R. Smith
Mr. and Mrs. Fred Snider
Mrs. John T. Snite
Mr. Charles L. Snow
Anastasia D. Zolas
Ms. Mary C. Soares
Mrs. David R. Somerville
Mrs. Lloyd H. Southworth
Betty L. Springer
Sam S. Stein
D. Yvonne Stevens
Joan M. Stevens
Mr. Floyd M. Stevenson
Ms. Joan Stevenson
Mr. Fred Stoops
Ms. Elizabeth T. Storz
Mr. and Mrs. Wilbur J. Strohm, Jr.
Frank and Norma Sugg
Mrs. Elizabeth V. Sullivan
Ms. Elizabeth Lowell Sutton
Ms. Clare Swarthout
Ms. Ruth Walker Sweeney
Mr. Frank M. Swirles
Mr. Steven K. Taft
Dr. S. Jerome and Judith D. Tamkin
Mildred L. Taylor
Mr. Harold J. Temkin
Mr. and Mrs. William R. Teran
Mr. and Mrs. Frank R. Tharp
Elsa Tingle
Dr. and Mrs. John S. Trombold
Mr. and Mrs. Reginald W. Twiggs
Dr. William G. Van Dorn
Major Frank Van Oosbree
Mr. and Mrs. Robert Vanderhagen
Theodore H. Vandling
Mrs. Myron C. Vincent
Ms. Dorothy O. Vogler
George R. and Nancy A. Von Arx
Ms. Lisette Wagaman
Mr. William Waite
Mrs. Norton S. Walbridge
Ms. Martha E. Walbridge
Mrs. Margaret M. Wallace
Mr. Robert G. Wallace
Carmen W. Walsh
Lillian R. Waltz
Ms. Carolyn A. Wardell
Mr. and Mrs. Thomas N. Warner
Ruth L. Warshaw
Bradford F. and Margot M. Washburn
Mr. and Mrs. Vernon Waters
Miss Dorothea E. Watkins
Dale E. Watson
Marjorie B. Watters
Mr. and Mrs. Dick Webber
Dr. and Mrs. Charles E. Weber
Mrs. Robert I. Weber
Mrs. Walter J. Weil
Mr. and Mrs. Louis Weinstock
Mr. and Mrs. Milton F. Weiss
Mr. and Mrs. John Weld
Dorothy Welker
Margaret L. Whittemore
Hans and Dagny Wiener
Mr. and Mrs. James R. Williams
Ellen Willie
Mrs. Charles N. Wilpan
James Gould Wilson

A Vision Realized | **In December of 1989 the W. M. Keck Foundation awarded a significant grant to TSRI "To support the addition of a distinguished senior chemist to the Department of Chemistry." That senior chemist was K. Barry Sharpless, Ph.D., recipient of the 2001 Nobel Prize in Chemistry. The continuation of Dr. Sharpless's work at this institution has enriched and enlarged the vision of biologists and chemists immeasurably. The role of the Keck Foundation in helping to bring our institution to the forefront of biological chemistry today is recognized throughout TSRI.**

Ms. Minta D. Wilterding
Dr. and Mrs. Merlin E. Woesner
The Rt. Rev. Robert M. Wolterstorff
Mr. Ralph C. Woodard
Dr. and Mrs. Ewart H. Wyle
Margaret C. Yager
Ms. Sandra Ann York
Mrs. Carolyn W. Yorston
Mr. and Mrs. John T. Zeien
Ms. Janet C. Zipter
Ms. Adele J. Zirinsky

Opportunities for Giving

Unrestricted Funds

The success of any research institution rests in its ability to identify promising new research programs in their infancy. Unfortunately, new programs generally do not qualify for federal grant support until they are fully developed. Similarly, young scientists who have not yet achieved prominence are also at a disadvantage in competing for grants. Their search for funds is apt to delay their work and inhibit them from striking out in new directions. Consequently, unrestricted gifts constitute one of our most valuable resources as they allow us to underwrite important new projects that might not otherwise receive funding.

Giving Opportunities | Gifts of all sizes are welcome. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council.

Immunology Department

In 1961, internationally acclaimed immunologist Dr. Frank J. Dixon, Jr., arrived at the Scripps Clinic and Research Foundation (SCRF) to begin investigations that would be the genesis of The Scripps Research Institute. Dixon brought with him his entire pathology department from the University of Pittsburgh to establish the Department of Experimental Pathology and begin SCRF's research program — later evolving into the Research Institute of Scripps Clinic — in the fledgling field of immunopathology.

Dixon's small group of investigators were primarily interested in the underlying biology of autoimmune diseases and immunologic diseases, and their highly successful initial studies developed a conceptual framework to explain how normal, but inappropriate, immune reactions give rise to both local and inflammatory diseases. The research program subsequently expanded to include basic investigations of both the innate and acquired immune systems, cancer immunology, immunology of infectious diseases and intracellular signaling mechanisms.

Today, more than ever, the ability to manipulate the immune system is vital to improving health. Thus, our scientists focus on studies that may lead to practical and effective solutions to many world-wide health problems, including some of the most puzzling diseases of our century: lupus, diabetes, arthritis, prion disease, HIV, Ebola virus, bacterial meningitis, chronic inflammatory disease, cancer and many others.

TSRI has a one-time opportunity to purchase the building in which the Immunology Department resides from the building owner. This building, designed specifically for TSRI laboratories, houses many of the world's leading immunologists. TSRI plans to partially finance the purchase of the building with a new bond issue, as we have done for our other facilities. The remainder of the cost of the building must be obtained from private, non-Federal sources. A naming gift will assure a donor a high level of recognition in the world of biomedical science.

Giving Opportunities | Naming opportunities are available as follows:

Building	$ 5,000,000
South Campus	$ 3,000,000
Laboratory Floor	$ 1,000,000
Individual Laboratory	$ 75,000
Large Conference Room	$ 200,000
Small Conference Room	$ 100,000

Institute for Childhood and Neglected Diseases

The Institute for Childhood and Neglected Diseases at The Scripps Research Institute applies the new molecular understanding of biology to address, reduce and successfully treat illnesses in two major categories — childhood diseases, including childhood cancers, and neglected diseases that affect populations primarily in developing countries.

The time has come to apply the burgeoning knowledge of genes to specific childhood and early-onset diseases. For a number of years, researchers have attempted to use new therapies like gene therapy against many of these diseases — cystic fibrosis and muscular dystrophy, for example, and certain forms of cancer. Unfortunately, none of these efforts has led to consistent success. But in each case, there is reason to believe that the work done thus far has laid the groundwork for approaches that will succeed. And in other cases, such as autism, scientists are only now uncovering genetic clues that might lead to better treatments.

The majority of the world's population lives in developing countries, and has yet to reap the benefits of the genetic revolution. As biologists have begun to learn how human genes function, they also have begun to investigate the genes of parasites and other disease-causing organisms. The Institute for Childhood and Neglected Disease will build on TSRI's previous successes, and will use the latest advances in biology to help vanquish parasitic diseases.

Giving Opportunities | Gifts of all sizes are welcome. Some naming opportunities are still available. A commitment of $150,000 will establish a senior research fellowship that supports the work of a senior scientist for two years at the Institute. A commitment of $50,000 will support a laboratory that will bear the name of the donor or loved one.

The Helen L. Dorris Institute for the Study of Neurological and Psychiatric Disorders of Children and Adolescents

The Helen L. Dorris Institute for the Study of Neurological and Psychiatric Disorders of Children and Adolescents was recently established with another generous gift from mental health advocate and SDSU emeritus, Helen L. Dorris. This new initiative was launched to uncover the pathological basis of neurological and psychiatric disorders and to enable therapeutic approaches to be developed. Benjamin Cravatt, Ph.D., director of the new Institute, will be leading the effort to recruit an interdisciplinary team of scientists to focus on understanding neuropathology in children and adolescents.

Giving Opportunities | Gifts of all sizes are welcome. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council. A commitment of $150,000 will establish a senior research fellowship that supports the work of a senior scientist for two years at the Institute. A commitment of $50,000 will support a laboratory that will bear the name of the donor or loved one.

Faculty Chairs

An endowment gift to establish a named faculty chair at TSRI is one of the most meaningful, and lasting, gifts available to the private donor. Such a gift perpetuates the donor's philanthropy by creating a permanently funded position, named by or for the donor, which may be occupied in succession by major figures in the world of biomedical science. The benefits far outlast the life of the donor, and will be enjoyed by successive generations of family members.

Giving Opportunities | A commitment of $1,500,000 will establish a senior faculty chair bearing the name of the donor or loved one. A commitment of $2,000,000 will establish a named faculty chair to be occupied by a Dean, Director or Department Chair.

Senior Research Fellowships

Sometimes the implications for discoveries in basic research are unknown. Often, though, discoveries by geneticists, neuroscientists, immunologists and other basic scientists become the foundation for the most important breakthroughs in medical treatments and diagnostic technologies.

A gift to fund a senior research fellowship provides a scientist with the opportunity to pursue new directions that would have been otherwise left uncharted and could possibly lead to better therapeutics and medical advances. Funding a senior research fellowship would also be a great way of participating in one of the great scientific adventures of our time.

Giving Opportunities | A commitment of $75,000 or more will establish a senior research fellowship that supports the work of a faculty member or a senior scientist for one year. A gift in the amount of $1,250,000 or more will endow a senior research fellowship ensuring the ongoing funding of a scientist's research work or initiative.

Harold L. Dorris Neurological Research Center

The Harold L. Dorris Neurological Research Center was founded in 1999 as the result of a major naming gift and long-term commitment by the Harold L. Dorris Foundation under the direction of Helen L. Dorris.

The Center is bringing a dedicated effort to conducting research and education into neurological disorders, including schizophrenia and Alzheimer's disease, as well as advancing knowledge of the process of aging of the brain. The Center has attracted an international cadre of brain scientists, led by Tamas Bartfai, Ph.D. Dr. Bartfai is former head of central nervous system research at Hoffman-LaRoche in Basel, Switzerland, and former chairman of the Department of Neurochemistry and Neurotoxicity at Stockholm University.

The Center seeks contributions to supplement the original gift of $10 million to recruit additional senior faculty, establish named fellowships and create visiting professorship appointments.

Giving Opportunities | Contributions of all sizes are welcome. A gift of $1,500,000 will permanently name and support faculty chairs while a gift of $1,250,000 will endow and name a senior research fellowship and a gift of $50,0000 will establish a visiting professorship. Specific program funding in the range of $50,000–$300,000 for new scholars is also a priority.

Graduate Degree Program

In 1989, The Scripps Research Institute (TSRI) established a Ph.D. program in Macromolecular and Cellular Structure and Chemistry. A second Ph.D. program in Chemistry was established three years later to focus on synthetic and bio-organic chemistry. Taken together, these programs provide an exceptional training opportunity in a unique learning environment for a select group of outstanding and intellectually diverse students.

We believe that The Scripps Research Institute's philosophy toward education, emphasis on individualized instruction, adherence to the highest scientific standards, and reputation for research excellence provide an unparalleled environment for advanced study and outstanding preparation for successful careers in science.

Giving Opportunities | Contributions of all sizes are welcome. A gift of $22,500 will name and support a graduate stipend for one year. A commitment of $10,000,000 will endow the Graduate Program and will entitle the donor to name the program.

Summer Research Internship and Teachers Training Program

In 1989 The Scripps Research Institute established a summer internship program for students from local high schools. This initiative was designed to give high school students, undergraduate students and middle and high school science teachers an intensive, basic hands-on science research laboratory experience.

Since 1993, over 220 high school students have participated in the Summer Research Internship Program. During the same time, nearly 30 science teachers and 77 undergraduates from local colleges and universities have attended the program.

At this time, the program capacity has grown to as many as 50 internship slots each summer. With the demand and popularity of this program in local high schools, one of the limiting factors on filling these slots is availability of funding. In addition, we have developed a teacher high school component, which will considerably enhance the teaching of sciences in the high schools themselves.

Giving Opportunities | Contributions of all sizes are welcome. A contribution of $2,500 supports the participation of one high school or undergraduate student in the summer program. A contribution of $5,000 supports the participation of one teacher in our Teacher Training Program or can fund a One Day Teacher Training Seminar on Contemporary Issues in Bioscience. A contribution of $1,000,000 can name and endow the entire program.

Endowments

The Scripps Research Institute seeks to enhance its endowment base from private contributions to provide ongoing income each year that can replace federal support. An endowment gift is one of the most meaningful, and lasting, gifts available to the private donor. The benefits far outlast the life of the donor, and will be enjoyed by successive generations of family members.

Giving Opportunities | A gift of $1,500,000 or more will permanently name and support a senior-level faculty position while a gift of $2,000,000 will establish a named faculty chair to be occupied by a Dean, Director or Department Chair.

Other endowment opportunities exist throughout the institute's departments and centers. Specific programs such as the High School Student and Teacher Science Training Program can be endowed with gifts of $100,000 and up, and will be tailored to the donor's interests and wishes within the programmatic priorities of the institute.

Equipment Acquisition

TSRI enjoys one of the world's leading private computational capabilities with an array of computers, including a Cray supercomputer. Research is further supported by X-ray crystallography laboratories, high performance NMR spectrometry including state-of-the-art 900 and 750 MHz instruments, electron microscopy, optical spectroscopy, a centralized DNA sequencing laboratory and a fluorescence activated cell sorting facility. Scientists are able to make new discoveries and advances in research with the help of modern technology.

TSRI scientists require state-of-the-art facilities and equipment to remain on the cutting edge of research and rapidly changing technology. New laboratory equipment and tools are constantly being developed to improve the efficiency and effectiveness of the scientists. Gifts of discretionary funding are needed to fund the continuous modernization of laboratories and equipment at TSRI.

Giving Opportunities | Gifts of all sizes are welcome. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council.

The Kresge Library

The present collection of the Kresge Library has its roots in the Medical Library established with the founding of Scripps Metabolic Clinic in 1924. At that time, the key reference tool used to identify relevant scientific and medical publications was the printed index. Since its founding, the Library has maintained subscriptions to three major indexes: Biological Abstracts which dates from volume 1, 1927; Chemical Abstracts which is complete from 1907 to present; and the print predecessors to today's Medline database which date from volume 1, 1916. Science Citation Index was added in 1975 to provide Scripps scientists and physicians with access to the unique advantages offered by citation indexing.

The Kresge Library is currently undertaking a major effort to expand access to these indexes electronically and making them

available at the scientist's desktop. Private support for the Library is needed to take advantage of technological advances, and to purchase tools for students and faculty to manage the explosion of scientific and medical publishing. These tools are essential to the central mission of TSRI, which is to build on the existing base of knowledge and to rapidly disseminate new findings to the scientific community.

Gifts of discretionary funding are needed to fund the revamping of the Library. The Library's furnishings, specifically its study carrels and chairs have served generations of students and faculty and are in need of replacement.

Giving Opportunities | Gifts of all sizes are welcome. A gift of $100,000 or more will provide for the purchase of the electronic version of an index, thereby greatly expanding access. A contribution of $20,000 or more will refurbish the Library with new study carrels and chairs. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council.

Gifts to The Scripps Research Institute

Gifts to The Scripps Research Institute (TSRI) provide the assurance that our institution will continue its mission of striving for excellence in biomedical research. Unrestricted gifts are particularly useful as they can be applied to programs and areas of urgent need. Gifts may also be designated for specific purposes, such as research, educational programs, or equipment. They may also be made in tribute to or in memory of a relative or friend.

Gifts of Cash

An outright gift of cash is usually the simplest method of giving. It is not subject to gift or estate taxes, and you can deduct the gift amount from your federal income tax return up to 50 percent of your adjusted gross income. Should the gift total exceed your gift ceiling for that year, you can carry over the remaining deduction to succeeding tax years. This means that with careful planning, nearly every outright gift to TSRI can be fully deducted.

Gifts of Securities

Giving appreciated stocks or bonds is a superb way to show support for the institution. You can deduct the full fair market value of long-term appreciated securities, and avoid any tax on the capital gain. A gift of securities is deductible up to 30 percent of your adjusted gross income, with the five-year carryover option. Under certain circumstances, however, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation in the contributed property—that is, to the cost basis.

Gift of Real Estate

Almost any type of real property—a personal residence, a farm, a vacation home, a commercial building, or an undeveloped parcel of land—can constitute a gift. A gift of real estate can be made either outright or through other methods.

If the property has appreciated in value and is given outright, you will avoid any tax on the capital gain, reduce your taxable estate by the value of the gift, and receive a charitable contribution deduction for 100 percent of the fair market value of the property. Your actual income tax savings will depend on your tax bracket. You may deduct the value of the gift up to 30 percent of your adjusted gross income. Under certain circumstances, however, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation—that is, to the cost basis.

Gifts of Residence

The tax laws enable you to donate your personal residence or ranch and still live there for the remainder of your life. Furthermore, you can stipulate that your spouse may live there for his/her lifetime, or you may continue to live on the property for a set number of years. Either way, you will receive an immediate income tax deduction for the contribution. The property does not have to be your primary residence—it can be a vacation or second home. Further, you do not have to reside on the property. You can also give stock in a cooperative apartment if the apartment is used as a primary residence. The charitable deduction is less than the full value of the property and equals the value of the remainder interest given to us. There are also charitable deductions available for estate or gift tax purposes if the life interest is given to one or two individuals and the remainder interest given to charity.

Gifts of Undivided Interest in Property

You are allowed a charitable deduction for the value of an undivided portion of your entire interest in a property. This consists of a fraction or a percentage of each substantial right or interest in the property. The fraction must extend over the entire term of your interest.

Gift by Bargain Sale

This entails your transferring ownership of an appreciated asset (real estate, securities and the like) to TSRI. In return, we

would pay you an agreed-upon amount that is less than the full fair market value—usually your original cost. Essentially, you are selling your asset to us for less than its fair market value, so the transaction is part gift and part sale.

You might want to consider this method if the current value of the property exceeds the amount you wish to give or if it is not practical or economical to divide the property. You are entitled to a charitable deduction based on the difference between the sale price to us and the full fair market value. You incur tax only on the part of the appreciation attributable to the sale.

Gift of Life Insurance

Sometime you may reach a point where life insurance no longer has the financial significance for your family that it once did. In that case, you may wish to make a gift of the policy to TSRI. There are two ways to do this.

First, you may make TSRI the owner of the policy. This allows you an immediate income tax deduction. If the policy is fully paid up, your deduction is equal to the replacement value of the policy unless that value exceeds the tax or cost basis. If premiums remain to be paid, the deduction is approximately equal to the cash surrender value. If you continue to pay the premiums on such policies, you will be entitled to a charitable contribution deduction. Or you may wish to contribute the amount of the premiums to us; we, in turn, could pay the premiums. As long as we are not under any obligation to pay the premiums, your contribution would be fully deductible.

Secondly, you also may name TSRI as the beneficiary of your policy. Since the designation is revocable it cannot be counted for any immediate tax savings. At your death, however, your executor may take federal estate tax charitable deduction for the entire amount.

Life insurance interacts well with other gift mechanisms. For instance, you can use all or part of your trust or annuity income to establish an irrevocable life insurance trust. The trust could purchase insurance on your life—perhaps an amount equal to the charitable gift—and you could name a spouse or child as the beneficiary. This way you can make a charitable gift and replace the assets with life insurance for the benefit of a loved one.

Alternatively, you could take all or a portion of the income for a set term of years and purchase a universal life insurance policy naming a family member the beneficiary. This is another excellent way to replace the wealth transferred to charity.

Life Income Gift

Another way to make a gift to TSRI is to transfer property (e.g., cash, securities, real estate) to the management of a trustee (for example, TSRI as an independent agent), and establish a life income arrangement. After the lifetimes of the beneficiaries, we receive the assets in the trust. Life income trusts provide many benefits to you as a donor: an income tax charitable deduction, a reduction in estate taxed, avoidance of capital gains taxes, freedom from investment worries, and, of course, income for life.

There are several types of life income arrangements for different circumstances: unitrust, annuity trust, pooled income fund, gift annuity. Information about each gift arrangement is readily obtained from the Development Office at TSRI.

Gift in Trust-Wealth Transfer

A trust may be funded with property (e.g., cash, securities, real estate). The terms of the trust will provide for specific payments to TSRI for a number of years, after which the property is passed to a relative or friend of the donor. The donor receives sizeable estate and gift tax advantages, and TSRI immediately receives funds for its programs. This arrangement is called a lead trust.

Corporate Matching Gift

Many companies encourage philanthropic giving among their employees by offering to match an employee's gift with a corporate contribution. Donors interested in this opportunity should obtain the necessary matching gift form from their employer (usually the personnel office).

Gift by Bequest

One of the easiest and most common ways to make a gift to us is through a bequest in your will. The tax laws encourage bequests; consequently, a bequest is an excellent way to support our programs. Bequests work particularly well for those who are unable to make an immediate outright gift, but would like to aid us in the future. There are several types of bequests:

- Specific bequests take the form of an outright gift of money, securities or other property.
- With a residuary bequest, we can receive the residue of your estate after all other bequests have been made.
- A contingent bequest takes effect only in the event that all other bequests, for whatever reason, fail.
- A bequest may also take the form of a testamentary trust; to receive the tax benefits, however, the trust must either

be solely for charity or be a qualified charitable remainder or lead trust.

When you make a bequest to us, your taxable estate is reduced by a 100 percent deduction for the amount of a cash bequest, or the fair market value of appreciated assets.

This deduction results in tax savings whenever the taxable estate — after other deductions — exceeds the amount offset by individual estate tax credits. Because the estate tax rate schedule is progressive, the larger the taxable estate, the greater the potential tax savings per dollar given.

For more information regarding any of these ways of giving, please contact:

Denise M. Scalzo
Director of Development
The Scripps Research Institute
10550 No. Torrey Pines Rd
Mail Drop TPC-2
La Jolla, CA 92037
(858) 784-9365
(800) 788-4931
(858) 784-2608 FAX

Benefits of Giving

For a one-time gift or cumulative gifts of the designated amounts you receive these benefits:

$200,000

- Life Benefactor status, with your name listed on the Honor Roll Boards in the lobbies of all Scripps Health Hospitals
- Continuing membership in the Scripps Presidents' Council (see section that follows for a complete description of this program)

$100,000

- Life Benefactor status, with your name listed on the Honor Roll Board
- Continuing membership in the Scripps Presidents' Council

$50,000

- Benefactor status, with your name listed on the Honor Roll Board
- Continuing membership in the Scripps Presidents' Council

$25,000

- Associate status, with your name listed on the Honor Roll Board
- Continuing membership in the Scripps Presidents' Council

$10,000

- Guarantor status, with your name listed on the Honor Roll Board
- Annual membership in the Scripps Presidents' Council for the year following a gift of $1,000 or more

$5,000

- Sponsor status, with your name listed on the Honor Roll Board
- Annual membership in the Scripps Presidents' Council for the year following a gift of $1,000 or more for any purpose

Scripps Presidents' Council

Founded in 1984, the Scripps Presidents' Council was created to serve two basic objectives: first, to provide a perpetual source of private resources for new and ongoing medical and research programs; and second, to provide a medium for sharing the excitement of our programs with those who invest in these undertakings.

Annual membership in the Scripps Presidents' Council is extended to individuals who contribute $1,000 or more in a given year. Those who have contributed $25,000 or more on a cumulative basis, or who make provisions for a bequest of $250,000 or more, receive membership benefits in perpetuity. Gifts may be earmarked for either specific research purposes, or left undesignated for use where the need is greatest.

Special privileges unique to the Scripps Presidents' Council are extended to all members:

- On request, personal assistance from a member of our Development Office regarding medical services at a Scripps Health hospital or informational needs
- A personalized yearly report outlining the impact of your gift
- The Scripps Presidents' Council Special Event, an exclusive annual gathering
- Special invitations to scientific briefings, receptions and lectures where fellow members meet to learn more about the vital work their contributions support
- Scripps Foundation Annual Report, which includes a listing of all Scripps Presidents' Council members
- A membership card listing the Scripps Health Information Line telephone number for immediate information concerning patient appointments and physician referral
- Selected press releases on topics of general interest sent to help keep all members informed about TSRI's newsworthy activities
- Scripps Foundation quarterly newsletter *update*, that

discusses developments at The Scripps Research Institute, the latest clinical procedures available to our patients, and overall advances made at TSRI and Scripps Health

- TSRI Scientific Report, an annual report of scientific progress, awards received, and publications made by TSRI scientists.

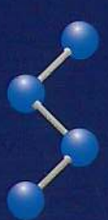
And, of course, the satisfaction members receive from knowing they have personally contributed to the advancement of medical knowledge through their gifts.

If you are interested in joining the Scripps Presidents' Council, please contact:

Denise M. Scalzo
Director of Development
The Scripps Research Institute
10550 No. Torrey Pines Rd
Mail DropTPC-2
La Jolla, CA 92037
(858) 784-9365
(800) 788-4931
(858) 784-2608 FAX

A publication of the
Office of Communications
The Scripps Research Institute

Editor:
Robin B. Goldsmith
Writers:
Jason Socrates Bardi
JoAnn Anderson
Design:
Sandra Sharp
Greenhaus
Production:
Janet Juliano
Jennifer O'Sullivan
Photography:
Jeff Tippett
Printing:
Bordeaux Printers, Inc.



THE SCRIPPS RESEARCH INSTITUTE

10550 North Torrey Pines Road, La Jolla, California 92037 858.784.1000 www.scripps.edu