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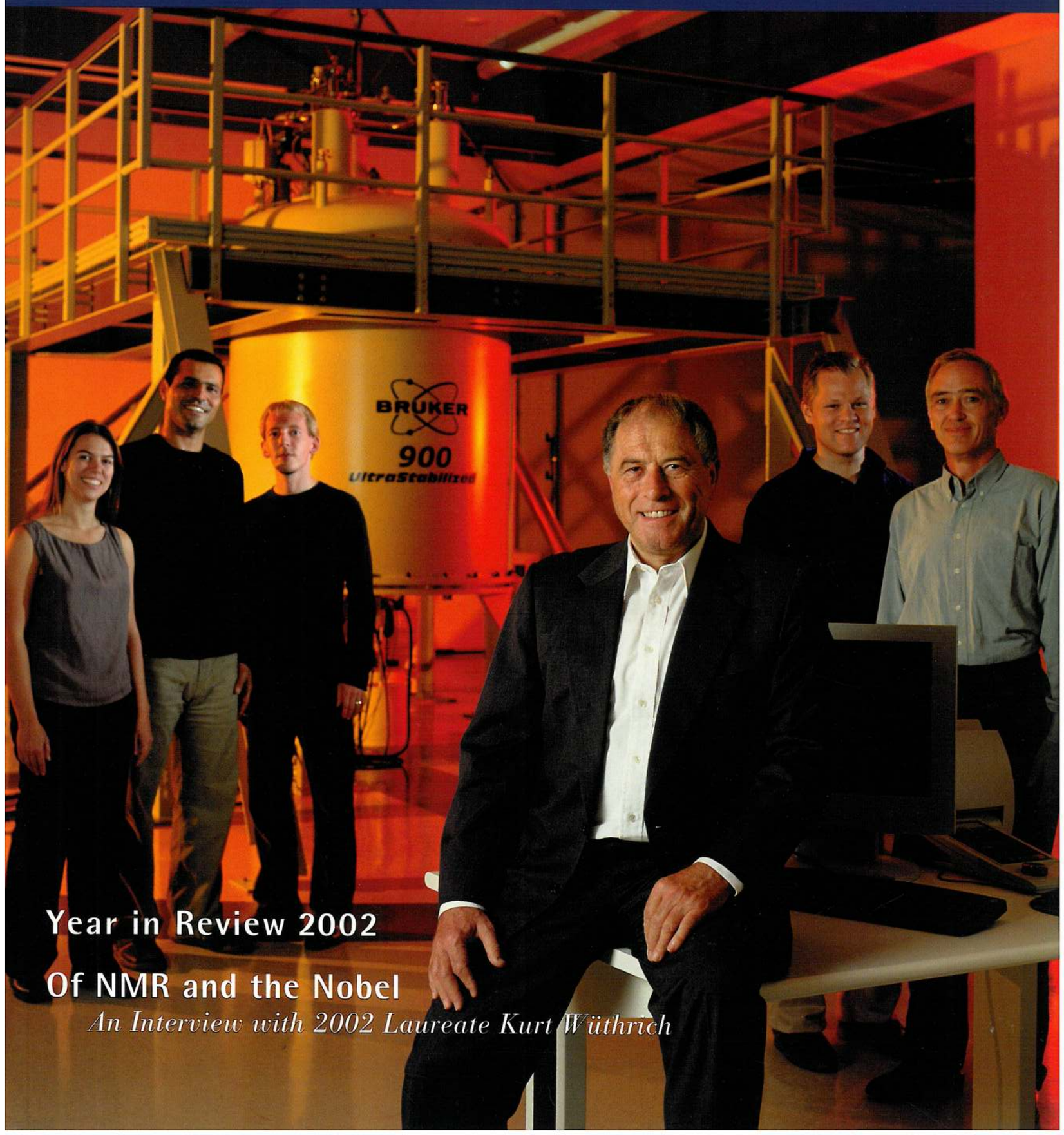
THE SCRIPPS RESEARCH INSTITUTE

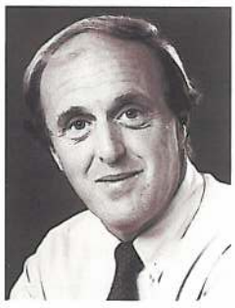
Endeavor



Year in Review 2002

Of NMR and the Nobel

An Interview with 2002 Laureate Kurt Wüthrich



It is a great honor to congratulate Kurt Wüthrich, visiting professor of The Scripps Research Institute (TSRI) and member of The Skaggs Institute for Chemical Biology, on receiving this year's Nobel Prize in Chemistry for his work in applying nuclear magnetic resonance to solving the structures of biological macromolecules. Currently also a professor of biophysics at Eidgenössische Technische Hochschule Zürich, in Switzerland, he is scheduled to become a full-time faculty member at TSRI in 2004. A true pioneer in the field, Kurt continues to push the boundaries of structural biology in new and innovative ways. In an institution in which structural work plays such a pivotal role, Kurt's presence creates extraordinary opportunities for increased collaborations across numerous disciplines.

It seems that each year brings with it a new scientific initiative at TSRI, and this year is no exception. In April, the Center for Integrative Molecular Biosciences opened at the institute, bringing together the talents of several research groups with seemingly divergent interests in chemistry, biochemistry, structural biology, and cell biology. What unites the members of the new center is their interest in the combined use of x-ray crystallography and electron microscopy as a means to unravel the structure and mechanism of action of the large molecular assemblies of the cell. The centerpiece of the facility, which is directed by Ron Milligan, professor, Department of Cell Biology, is a suite containing six state-of-the-art electron microscope rooms, a unique feature that makes the facility one of the most advanced biological microscopy centers in the world.

TSRI's graduate studies program continues to be ranked among the top in the country, according to a study by *U.S. News & World Report*. The publication ranked the program sixth overall in chemistry, second in the specialty of organic chemistry, ninth overall in the biological sciences, and sixteenth in the specialty of biochemistry. That a program launched only 13 years ago can successfully compete with the most established graduate schools in the country is testimony to the extraordinary leadership of the founding dean, the late Norton B. Gilula, and of its current dean, Jeffery Kelly.

This year the graduate studies program took on a name that is synonymous with excellence in graduate education. In honor of their extraordinary contributions to TSRI, science, and education, the institute named the graduate college the Kellogg School of Science and Technology for philanthropists Janet R. (Jean) and W. Keith Kellogg II. For many years the Kelloggs have been not only great beneficiaries of TSRI but also two of the country's most devoted philanthropists, giving generously to several institutions of higher learning in California and the Chicago area. Locally, they established an endowed chair in chemistry at TSRI, made significant contributions to the Beckman Center for Chemical Sciences, and funded the continuing care unit at Scripps Memorial Hospital-Encinitas.

I continue to be impressed by the breadth of the research discoveries made by TSRI scientists, who have published their findings in more than 1,000 articles in prestigious peer-reviewed journals. Two scientists, John Yates and Laurence Florens, led a collaborative effort involving 18 researchers at numerous laboratories in the United States and the United Kingdom to determine the "proteome" of the most deadly form of the malaria pathogen. Knowing which proteins are expressed could help scientists understand how the parasite causes malaria and potentially how to thwart it. In a related study, researchers at TSRI and the Genomics Institute of the Novartis Research Foundation, San Diego, used a relatively new technology to detect markers in the DNA of the most deadly type of malaria pathogen. This discovery by Elizabeth Winzeler and her colleagues

On the Cover:

Kurt Wüthrich, who is with TSRI as Cecil H. and Ida M. Green Visiting Professor of Structural Biology and member of TSRI's Skaggs Institute for Chemical Biology, won the 2002 Nobel Prize in Chemistry. Wüthrich is shown here with some TSRI colleagues.

could enable scientists to identify the particular strain of malaria during an outbreak and determine if the strain is drug resistant. This work should make it easier for health officials to follow the spread of drug resistance around the world and develop strategies to deter this spread.

A group of TSRI scientists this year was awarded a five-year, $9.6-million grant from the National Eye Institute to study the leading causes of blindness and to develop treatments for patients with neovascular eye disease. Most diseases that cause catastrophic vision loss do so as a result of abnormal angiogenesis, the uncontrolled growth of new blood vessels. Currently, no effective treatment exists for most patients with these diseases, but researchers have been seeking compounds that could inhibit angiogenesis and reduce the vision loss associated with vascular proliferation, fluid leaking, and bleeding.

A new class of antiangiogenic molecules, which may be useful in the treatment of neovascular eye disorders, was described this year by Martin Friedlander and Paul Schimmel, lead investigators on the new grant, along with professor of immunology David Cheresh. In a related development, the Friedlander group discovered a way to use stem cells from the bone marrow of adults to form new blood vessels in the eye or to deliver chemicals that could prevent the abnormal formation of new vessels. The technique, which involves injecting the stem cells into the eye, could be used to stimulate vessel growth, address inherited degenerations of the retina, and treat ocular diseases due to abnormal retinal angiogenesis.

Peter Wright and Jane Dyson solved the structure of a protein crucial for the growth of tumors. Blocking the protein stops tumor growth in animal models, and the molecular details revealed by the structure will provide scientists with more information to develop future anticancer therapeutic agents. The protein, hypoxia-inducing factor, is a potential target for drugs that will stop tumor growth because it is extremely important for angiogenesis. In another study described in *Nature,* a group led by Dr. Wright solved the structure of two critical human proteins that are normally unstructured in the cell but fold synergistically, forming an active biological structure. This phenomenon, which had never been seen before, leads scientists to think that they can no longer merely equate structure with function. Further, the structures may lead to new therapies, because the proteins are important regulators of genes essential for development and reproduction and are implicated in cancer and other diseases.

Argyrios Theofilopoulos, a professor in the Department of Immunology, suggests a powerful new way to treat cancer. This method involves injecting fresh immune cells to replace the immune cells that die immediately after chemotherapy or irradiation. An injection of cancer cells at the same time serves as a kind of "immunotherapy," which induces the patient's immune system to attack existing colonies of those cancer cells. The study suggests that immunotherapy should be initiated shortly after chemotherapy or radiation therapy, because the reduction in the body's T cells is actually an advantage, helping the body to develop a strong T-cell response to the cancer.

Wendy Havran, an associate professor in the Department of Immunology, identified a major role in wound repair for a mysterious type of immune cell that resides mainly in the skin and gut: the γδ T cell. Her findings should be important for scientists who are interested in treating diseases that arise from epithelial cell disorders, including asthma, psoriasis, cancers, and inflammatory bowel disease. The study indicated that when skin is cut or damaged, keratinocytes, a common type of epithelial cell, release the antigen that is recognized by the γδ T cells, which then become activated. Once activated, the cells begin making a growth factor that binds to keratinocytes and other epithelial cells, helping the cells proliferate and leading to the closure of the wound.

Ernest Beutler, chairman of the Department of Molecular and Experimental Medicine, led one of the largest DNA-based genetic epidemiologic studies ever conducted, reviewing DNA and clinical data of some 41,000 patients, looking for the genetic disease hereditary hemochromatosis. Dr. Beutler concluded that although the mutation that causes the hereditary disease is common, the disease itself is rare, a finding that runs counter to conventionally held wisdom about the disease. Previously thought to be the most common genetic disorder of Europeans, hemochromatosis is a metabolic disorder in which excessive amounts of iron are deposited in the liver, pancreas, and other organs. It can lead to cirrhosis of the liver, diabetes, and cardiovascular disease; in the severe form, it can be lethal. Dr. Beutler's findings, obtained by working with the Health Appraisal Clinic at Kaiser Permanente in San Diego, recently were confirmed in a large Scandinavian study. In recent years, there has been much interest in the possible benefits of screening for mutations like the one that causes hemochromatosis in order to prescribe preventive therapy. However, the cost-benefit ratio of screening healthy populations for this disease appears to be dramatically different in light of the results of these studies.

Scientists in the Department of Chemistry and The Skaggs Institute for Chemical Biology identified human antibodies against *Bacillus* spores, including spores of the bacterium that causes anthrax. The research group led by Kim Janda showed, for the first time, that human antibodies can recognize spore surfaces, which suggests that the antibodies might make a powerful and convenient tool for detecting anthrax. Moreover, antibodies that bind to spores have implications for treating people exposed to anthrax. The antibodies could potentially be given for passive immunization; they would help clear spores from the body. And, because of the ease of producing and administering antibodies, this approach could be a simple and inexpensive therapy.

In an attempt to test a new general strategy for drug discovery, a research group led by K. Barry Sharpless, Nobel laureate, W.M. Keck Professor of Chemistry, and member of The Skaggs Institute for Chemical Biology, created a potent blocking agent against an enzyme implicated in Alzheimer's disease. The scientists used click chemistry, a modular protocol for organic synthesis developed by Dr. Sharpless, to make a drug-like molecule that blocks the neurotransmitter destruction caused by the brain enzyme acetylcholinesterase. Unlike the situation in existing methods, in click chemistry, the target itself is mobilized to play a decisive role and select the final synthetic step. In this instance, the enzyme catalyzed the reaction that created its own inhibitor, resulting in the most potent inhibitor ever discovered for this widely studied brain enzyme.

Using a combination of chemistry and molecular genetics, members of The Skaggs Institute have discovered a way to attach a wide range of molecules to the surface of a virus, essentially enhancing the virus with the properties of those molecules. John E. Johnson and M.G. Finn's work may lead to the ability to build circuits of conducting molecules on the surface of viruses, forming a component of a molecular-scale computer, or a new type of "nanowire." In addition, the work may find applications in materials science, medicine, and molecular electronics. The technique can be used to immobilize large molecules, even whole proteins, on the viral surface.

Numerous members of TSRI's faculty were recognized this year for their scientific achievements. Two TSRI researchers, Francis Chisari and Chi-Huey Wong, were elected to membership in the National Academy of Sciences, bringing the number of members of the academy at the institute to 16. Membership in the academy is one of the highest honors that can be bestowed on members of the scientific community. In addition, Dr. Chisari was elected to the American Academy of Microbiology, K.C. Nicolaou received the Tetrahedron

Award, Dr. Nicolaou and his former graduate student Philip Baran were given the Nobel Laureate Signature Award for Graduate Education in Chemistry, Albert Eschenmoser received the Oparin Medal, and Julius Rebek was honored with the Chemical Pioneer Award. Ian Wilson was elected to the American Academy of Arts and Sciences; Ben Cravatt was named one of 100 young innovators in the United States by *Technology Review,* the magazine of the Massachusetts Institute of Technology; Eric Johnson was given the Brodie Award; Dale Boger received the Janssen Award; David Santoro was named recipient of the Burroughs-Wellcome Award; Mark Ginsberg received the Earl P. Benditt Award; Sandra Schmid received the Pinnacle Award from the Athena group at the University of California, San Diego; and I was given the Presidential Medal from the University of California and an honorary degree from Northwestern University. On an institutional level, TSRI was ranked second in the world among high-impact institutions in chemistry.

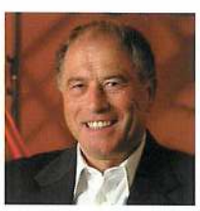
This year, five new members were added to TSRI's Board of Trustees: Gary N. Coburn, Thomas E. Dewey, Jr., Frank Lowy, Claudia S. Luttrell, and Ralph J. Shapiro. These new members strengthen the board with exceptional leadership ability, financial expertise, and solid business acumen. For more than 12 years before his retirement, Coburn worked at Putnam Investments in Boston, where he had overall responsibility for global fixed income investment policy, portfolio management, research, derivatives, and trading. Dewey is a member of McFarland Dewey & Co., a New York investment banking firm specializing in advisory and agency services for corporate and governmental clients. Lowy is executive chairman and cofounder of Westfield Holdings Limited, a public company that has been listed on the Australian Stock Exchange since 1960. Luttrell is a businesswoman, philanthropist, and community activist. Shapiro is chairman of Avondale Investment Company. We are thankful for their active participation and collective wisdom as they assist in guiding the future directions of the institute.

My kudos and congratulations to the members of TSRI's scientific community, and to the myriad technical and administrative support staff who work closely with them, for an extraordinary year of scientific accomplishment. At all levels, from graduate students to junior faculty members to senior investigators, from members of our core technical facilities to administrative directors, the level of commitment and achievement is extraordinary. Taken together, the collective enterprise, made possible by the contributions of the entire staff, is what makes TSRI such an exciting, vital, and dynamic place to conduct scientific research. There is reason for great optimism that it will remain so for many years to come.

Richard A. Lerner, M.D.

OF NMR AND THE NOBEL:
AN INTERVIEW WITH KURT WÜTHRICH

Kurt Wüthrich, Ph.D., was awarded the 2002 Nobel Prize in Chemistry "for his development of nuclear magnetic resonance [NMR] spectroscopy for determining the three-dimensional structure of biological macromolecules in solution."



Wüthrich, who is The Scripps Research Institute (TSRI) Cecil H. and Ida M. Green Visiting Professor of Structural Biology, member of TSRI's Skaggs Institute for Chemical Biology, and Professor of Biophysics at Eidgenössische Technische Hochschule Zürich (ETHZ), Switzerland, spoke with *Endeavor* magazine shortly after the prize was announced.

MANY PEOPLE HAVE DESCRIBED YOUR ACCOMPLISHMENTS RECENTLY; I WAS WONDERING IF YOU COULD DESCRIBE, IN YOUR OWN WORDS, THE WORK FOR WHICH YOU WERE AWARDED THE NOBEL PRIZE.

Well, we succeeded in establishing one-to-one relations between the individual peaks in the highly complex NMR spectra of proteins and the individual atoms within those proteins. This was the turning point in the field of NMR with proteins. From there on, the avenue was outlined for obtaining *de novo* three-dimensional protein structures. Getting sequence-specific NMR assignments in the early 1980s was about equivalent to solving the phase problem in x-ray crystallography by heavy atom replacements in the 1950s.

HOW IMPORTANT WAS IT THAT YOU WERE RECOGNIZED BOTH FOR THE TECHNOLOGY AND FOR THE STRUCTURES WHICH YOU SOLVED?

This probably reflects quite faithfully what happened. It was very important throughout the last three decades that our efforts in methods development were always guided by open questions that arose from working on interesting biological questions. The methodology to entertain these questions was often not available, so we were again and again motivated to return to methods development. Of course, I like to work with physicists on methods development. I also like to work with mathematical physicists and specialists in informatics

"...Our methods development was, at all times, guided by the need to solve yet another biological problem."

to develop the software that is needed. But it was important that these activities did not turn into a hobby, and that our methods development was, at all times, guided by the need to solve yet another biological problem.

AS A GRADUATE STUDENT TODAY ONE OFTEN HEARS THE ADVICE TO "CHOOSE A SYSTEM" RATHER THAN A TECHNOLOGY. BUT YOU CHOSE A TECHNOLOGY AND APPLIED IT TO MANY SYSTEMS THROUGH THE YEARS. DO YOU THINK THE SAME CHOICE WOULD BE WISE TODAY?

I think both choices can be the starting platform for a highly rewarding and successful career. Although focusing on a particular technique and on developing this technique further and further may appear to be a very limited project to pursue for a lifetime, I have, by the fact that we applied the technique in many different fields, had the chance to also gain knowledge and experience in biology and the biomedical sciences over the years. We would solve an important problem in immune suppression, and I would find myself a featured speaker at medical conferences on the subject. Or we would solve the structure of the homeodomain–DNA complex, and I would be a featured speaker at cell biology conferences. Then we would solve the structure of prion proteins, and I would find myself speaking to politicians, nutritional scientists, and again to medical doctors. This is all, of course, in addition to participating in specialized NMR meetings, since NMR is the trade that we bring to these other disciplines.

"My group is focusing on the emerging field of structural genomics."

DESCRIBE THE MOMENT WHEN YOU REALIZED THAT YOU WOULD BE ABLE TO SOLVE A STRUCTURE WITH NMR.

Well, this moment extended over a few years. I started NMR with proteins in 1967, when there were fewer than 10 papers in the field. About seven years later, in 1974, there were about 500 papers, but I felt that we were not making progress. At that point, I wrote the monograph, "NMR in Biological Research: Peptides and Proteins." The field was still so small that I could review the entire literature. And, by that, I recognized that we could not possibly ever solve a protein structure with the attempts that had been made—in my laboratory or in the others active in the field at the time. About a year after I had published this book, we worked with what is called the nuclear Overhauser effect (NOE). This is a physical phenomenon that depends on dipole-dipole couplings between individual nuclei and which obeys different rules in large molecules, which tumble slowly in solution, as compared to small molecules, which tumble rapidly. NOEs had previously been employed on a limited basis, and mostly with small molecules. The results that we obtained in 1976-77, using nuclear Overhauser effects, made it clear to me how we would determine *de novo* protein structures in solution.

Thus, while there is little mention of NOEs in my 1976 book, which was written in 1974-75, two years later it was clear to me how solving structures using NOE could be done. We actually went a long way with this in 1978, using the then-available one-dimensional NMR techniques. We were just doing bits and pieces of structures, but it was clear that the technique was going to work. It took another six years to develop, in collaboration with Richard Ernst (Nobel Prize in Chemistry, 1991), two-dimensional NMR methods for use with large molecules and then to develop the mathematical algorithms needed to compute three-dimensional protein structures from NMR data.

In 1984, we had arrived and solved the first structure.

WHICH WAS–

BUSI. Bull seminal trypsin inhibitor.

WHERE WOULD BIOLOGY BE TODAY WITHOUT NMR AS A STRUCTURAL TOOL?

There would be 3,000 fewer structures in the protein data bank. We would have quite a different feeling for the way protein molecules behave. We would not have any hands-on information on details of internal dynamics. We would have much less information on folding pathways of proteins, where much of the ground-breaking work has been done at TSRI by the groups of Peter Wright and Jane Dyson. We would not know about solvation of proteins in solution. Quite generally, we would miss a lot of information that is complementary to the data from structure determination by x-ray diffraction in single crystals.

YOU'VE ALWAYS SOUGHT TO EXPAND THE HORIZONS OF NMR, PUSHING THE DEVELOPMENT OF TECHNOLOGY

NOT JUST FOR YOUR OWN RESEARCH, BUT FOR THE FIELD IN GENERAL. WHAT ARE NMR'S CURRENT HORIZONS? WHERE IS IT GOING IN THE NEXT 10, 20 YEARS?

We have recently recorded NMR spectra of structures with a size close to one million Daltons, as documented in a *Nature* article about three months ago. So we now know that the spin physics enables us to use solution NMR over the entire size range from a water molecule to molecular structures with a mass of about one million Daltons.

Whether or not this size barrier will be further increased in the near future I would not want to guess; it is certainly not impossible. But it seems rather unlikely that there will soon be another step of a tenfold increase. Therefore, I think it will now be important to consolidate and to appreciate the available large window that includes a vast majority of all biological systems—considering just the size, of course. It will be a matter of refining the NMR techniques for large systems and of developing biochemical methods to prepare exciting systems for studies with NMR. There is now an incentive to introduce biochemical methods for partial isotope-labeling of proteins that were of no interest a few years ago, because one could not have studied, for example, segmentally labeled, very large molecular structures by NMR.

"I believe that a person who wants to become a good scientist has to have the moral strength of identifying with the project under study and of attaching the utmost importance to the daily work, without taking his/her person too seriously."

SO WITH SO MANY TARGETS TO CHOOSE FROM, HOW DO YOU SELECT WHICH TARGETS YOU'RE GOING TO TRY TO SOLVE?

Well, my group is focusing on the emerging field of structural genomics. In this field, one typically works with gene products for which no information on function is available. Therefore, it will be more and more important that, in addition to the determination of new protein structures with novel polypeptide folds, we are also able to obtain measurements that relate to the function of these molecules. I think the most important type of such information is data on intermolecular interactions with partners in the cell. NMR is a very powerful technique for such studies—thermodynamic measurements as well as kinetic measurements—in addition to structure determination.

WHY DID YOU CHOOSE TO COME TO SCRIPPS?

Well, my wife and I have always liked to live in California. We were at UC Berkeley as postdoctoral fellows in the 1960s. We have been back many times—here at Scripps, at Cal Tech, at Berkeley, at Stanford. Among all these distinguished schools, Scripps is a particularly attractive workplace for me and La Jolla is a very attractive place for my wife and myself to live.

SPEAKING OF YOUR FAMILY, HOW DO YOU BALANCE YOUR SCIENTIFIC CAREER WITH A BUSY FAMILY LIFE?

With my wife, I have an agreement that we do not take vacations. In turn, she often travels with me to scientific meetings. There are always days when there is free time for leisure activities, and I make special efforts that traveling to a scientific meeting with me is usually done at a comfort level that we would not necessarily afford if we took a private vacation. There is a mix of things that work this way, but I would definitely be very unhappy about "vacations" that would separate me for any length of time from my research activities.

HOW DID YOU BECOME INTERESTED IN SCIENCE?

This was much discussed in the Swiss press these last two weeks, because I also have a diploma as a sports instructor. In my youth, I taught skiing for many seasons; I was a swimming instructor; I taught sports in high school. I also taught physics in high school, and was planning to be a high school teacher in physics and sports.

Doing sports and scientific research, I had some

interesting things happening to me in the laboratory, so much so that I became a professor at the ETH Zürich at the age of 33. Before that I had been at Bell Telephone Laboratories in New Jersey, which was an excellent place to do research and where I also organized a soccer league. You see, over a time span of a few years I was sort of sucked out of sports into science.

"...it's great to have the opportunity to be at Scripps... I look forward to moving here permanently in 18 months and continuing my scientific work."

ARE YOU LOOKING FORWARD TO THE NOBEL CEREMONY ON DECEMBER 10?

Oh yes, of course. That will be a high point in my life.

HOW HAS WINNING THE NOBEL PRIZE CHANGED YOUR LIFE?

I think it has not changed my life in important ways up to this point, except that I am giving interviews more often than I have given interviews on average over the last few years. How it will be long-term, maybe we should talk about this two years from now...

WHAT ARE YOUR FAVORITE BOOKS?

I read the memoirs of Winston Churchill and memoirs of many famous scientists when I was in high school.

THE CHURCHILL MEMOIRS ARE VERY THICK.

Oh, I think 16 volumes.

YOU READ THE ENTIRE SERIES?

Oh yes. But that was when I was in high school.

CHURCHILL WON A NOBEL PRIZE IN LITERATURE FOR THOSE MEMOIRS IN 1953, I THINK.

Yeah? Very good. These last few years I have not been reading books very much. I mean, I'm using books a lot, but I'm not reading books. That's not the same thing.

HAVING WORKED WITH MANY SCIENTISTS IN YOUR CAREER, BEING A SCIENTIST YOURSELF, AND HAVING TRAINED MANY SCIENTISTS, WHAT ARE THE CHARACTERISTICS THAT MAKE A PERSON A GOOD SCIENTIST – OR ARE THERE SUCH CHARACTERISTICS?

Well, I believe that a person who wants to become a good scientist has to have the moral strength of identifying with the project under study and of attaching utmost importance to the daily work, without taking his/her person too seriously.

IS THERE ANYTHING ELSE THAT WE MISSED?

If there is anything to add, then it is just to say that it's great to have the opportunity to be at Scripps. It has been a great experience. I look forward to moving here permanently in 18 months and continuing my scientific work.

WELL, THANK YOU VERY MUCH. IT'S BEEN A REAL PLEASURE.

The ABCs of NMR

So what is nuclear magnetic resonance (NMR) spectroscopy anyway?

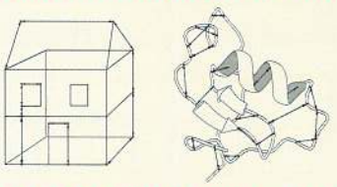
NMR is perhaps best-known as the technology behind the magnetic resonance imaging (MRI) machines found in today's hospitals. Doctors use MRI to scan patients and non-invasively view inside the body; similarly, scientists use a specialized, high-resolution NMR to scan test tubes filled with solutions of proteins, DNA, or other biological molecules to see what they look like.

Knowing the structure of molecules helps scientists understand how the body works. Moreover, structures are crucial to designing new and better drugs. In fact, there is no question that NMR is one of the most fundamental techniques in chemistry and biology today.

Discovered independently by two physicists in 1946—Edward Mills Purcell at Harvard University and Felix Bloch at Stanford University, who shared the 1952 Nobel Prize in physics for their discovery—NMR refers to the ability of atomic *nuclei* (the "N" of NMR) to absorb energy and reorient themselves in a *magnetic* field (the "M") when exposed to radiation of a particular *resonant* frequency (the "R") in the radio band.

Later, another Nobel, the 1991 Nobel Prize for Chemistry, went to Richard R. Ernst at ETH in Zürich for developing some of the fundamental tools used in NMR spectroscopy. Kurt Wüthrich has won the 2002 Nobel Prize in Chemistry for his contribution towards developing these tools and for extending NMR to biology—by determining the three-dimensional structure of biological macromolecules in solution.

Physically, NMR is possible because atomic nuclei in proteins and DNA behave like tiny magnets and tend to align themselves with a magnetic field—analogous to how a magnetic compass needle aligns itself with the North Pole.



KURT WÜTHRICH'S NOBEL PRIZE-WINNING WORK USES NMR TO DETERMINE THE THREE-DIMENSIONAL STRUCTURE OF BIOLOGICAL MACROMOLECULES. THIS PROCESS IS ANALOGOUS TO USING THE DIMENSIONS OF A HOUSE TO DRAW A PICTURE OF THAT HOUSE.

In an NMR experiment, a sample in a glass tube is inserted into the center of a "spectrometer." NMR spectrometers have extremely large and powerful magnets, and inside, the nuclei will align with the magnetic field. But an electromagnetic pulse of just the right frequency sent through the sample can cause the nuclei to realign. Then when the pulse is switched off, the nuclei reorient themselves. This reorientation causes small but measurable induced voltages, and it is this signal that is being measured in the NMR experiment. The NMR spectrometer scans such signals over a range of radio frequencies, and produces raw data, which is known as a spectrum. An NMR spectrum is unique for a particular molecule, and is influenced by the shape of the molecule in which the atoms reside. Thus NMR spectrometers can be used to solve the structures of proteins, DNA, or other important biological molecules. ■

BLOCH

PURCELL

ERNST

WÜTHRICH

IN THE LAST 50 YEARS, FOUR NOBEL PRIZES HAVE BEEN AWARDED FOR DISCOVERIES RELATED TO NMR.

Images of Bloch, Purcell, and Ernst courtesy of The Nobel Foundation.

MISSION *To understand the operations of living cells so that new therapies may be found for such ailments as cancer, heart, lung, muscle, retinal, and neurodegenerative diseases.*

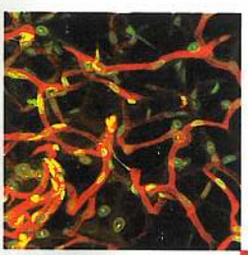
Cell Biology

2002 DEPARTMENT HIGHLIGHTS

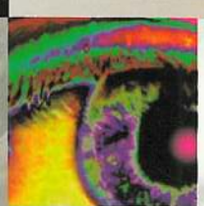
The work of four scientists in TSRI's Department of Cell Biology contributed to three of the top-ten breakthroughs of the year, according to the journal *Science*. PROFESSOR STEVE KAY, PH.D., who directs TSRI's Institute for Childhood and Neglected Diseases, conducted breakthrough work on "a new class of light-responsive cells in the retinas of mammals." ASSISTANT PROFESSOR ARDEM PATAPOUTIAN, PH.D., was mentioned for his work, which "helped explain why spicy food feels hot, and breath mints give the mouth a chill." And PROFESSOR JOHN YATES, PH.D., and ASSISTANT PROFESSOR ELIZABETH WINZELER, PH.D., both contributed separate research in support of the publication of "genome sequence drafts for organisms with major agriculture and public health relevance for the developing world." (See Research Highlights, next page.)

THE CENTER FOR INTEGRATIVE MOLECULAR BIOSCIENCES (CIMBio) opened in January. It recently received funding as a National Institutes of Health National Resource Center for Automated Molecular Imaging led by ASSOCIATE PROFESSOR BRIDGET CARRAGHER, PH.D., ASSOCIATE PROFESSOR CLINT POTTER, B.S., and PROFESSOR RON MILLIGAN, PH.D.

ASSOCIATE PROFESSOR MARTIN FRIEDLANDER, M.D., PH.D., PROFESSOR PAUL SCHIMMEL, PH.D. (Molecular Biology),



CHAIR: **SANDRA SCHMID, PH.D.** NUMBER OF PRINCIPAL INVESTIGATORS: **44** NUMBER OF OTHERS: **344**



MEMBERS OF THE DEPARTMENT OF CELL BIOLOGY INCLUDE CHAIR SANDRA SCHMID, PH.D., (LEFT), ASSISTANT PROFESSOR ARDEM PATAPOUTIAN, PH.D., AND 42 OTHER PRINCIPAL INVESTIGATORS. RESEARCH WITHIN THE DEPARTMENT HAS IMPLICATIONS FOR UNDERSTANDING A LEADING CAUSE OF BLINDNESS, THE GENETICS OF THE PARASITE THAT CAUSES MALARIA, CELL FUNCTION OF THE VASCULAR SYSTEM, AND PLANTS' SEASONAL RHYTHMS.

and a group of TSRI researchers, who recently discovered a potent inhibitor of angiogenesis, a process implicated in cancer and one of the leading causes of blindness, were awarded a five-year, $9.6-million grant from the National Eye Institute to study this inhibitor further and develop ways to use it in patients.

ASSOCIATE PROFESSOR BENJAMIN F. CRAVATT, PH.D., was selected as one of the top 100 innovators under the age of 35 in a special report released by *Technology Review*.

In a sweep for TSRI scientists at the American Society of Cell Biology meeting, Cravatt received the ASCB-Promega Award for Early Career Life Scientists, and ASSISTANT PROFESSOR CLARE WATERMAN-STORER, PH.D., was named the recipient of the ASCB Women in Cell Biology Jr. Career Recognition Award.

PROFESSOR AND DEPARTMENT CHAIR SANDRA L. SCHMID, PH.D., won a Pinnacle Award from UCSD Athena, in recognition of fostering personal and professional change through inclusion, risk taking, education, recognition, and diversity of thought.

PATAPOUTIAN was one of five Damon Runyon Scholars selected this year by the Damon Runyon Cancer Research Foundation.

THE VASCULAR BIOLOGY DEPARTMENT became a division of the Department of Cell Biology in 2002. The merger broadens the spectrum of research that takes places in Cell Biology and strengthens the department's commitment to research with important health implications.

2002 RESEARCH HIGHLIGHTS

KAY demonstrated that the gene *Opn4*, which codes for the protein Melanopsin, is the elusive pigment gene that captures light and keeps your body tuned to a daily cycle. Finding the key protein in the eye that sends signals to the body's internal clock has implications for sleep disorders, jet-lag, and shift work.

In addition, KAY and RESEARCH ASSOCIATE MARCELO YANOVSKY, PH.D., described how a plant grown in their laboratory uses two sets of proteins to detect the seasons so that it can flower at the right time. And by tinkering with those proteins, the scientists were able to make the plant flower at will.

PATAPOUTIAN identified and isolated a protein, called TRPM8, that mediates the body's ability to sense cold and menthol through the skin. TRPM8 is the first cold-sensing molecule that has ever been identified and may be an important basic target for pain-modulating drugs. He also identified and cloned the first-known gene that makes skin cells able to sense warm temperatures.

YATES led a team of scientists who identified the proteins in the most deadly form of the malaria pathogen, the single-celled *Plasmodium falciparum*. This accomplishment caps the completion of a major six-year $17.9-million effort that sequenced the entire *Plasmodium falciparum* genome.

WINZELER and scientists at Harvard University and the Genomics Institute of the Novartis Research Foundation found a way to use a relatively new but readily available technology to quickly detect markers in the DNA of the most deadly type of malaria pathogen. The technology could enable scientists and public health workers to identify a particular strain of malaria and determine whether it is drug resistant.

A promising target for the development of pain medication was provided by the CRAVATT lab, which solved the structure of an enzyme called fatty acid amide hydrolase that modulates central nervous system functions such as pain perception, cognition, feeding, sleep, and locomotor activity.

WATERMAN-STORER, PROFESSOR VELIA FOWLER, PH.D., and PROFESSOR MARK GINSBERG, M.D., have unraveled three critical aspects of how cells regulate and mobilize their cytoskeletons to drive cell migration. Waterman-Storer identified a kinase that ensures the coordinated assembly and disassembly of the two major cytoskeletal elements, actin filaments and microtubules. Fowler identified a protein, TmodE, which controls actin assembly at the leading edge of migrating cells. Ginsberg revealed new mechanisms of crosstalk between cell surface integrins that mediate cell attachment with regulation of actin assembly. Cell migration is critical for wound repair, angiogenesis, development, and cancer metastasis. ■

MISSION *To expand knowledge in the molecular sciences and apply it to the betterment of mankind—particularly by facilitating biomedical research—and to educate young men and women in these fields. The Department of Chemistry's areas of strength include chemical synthesis, bioorganic chemistry, and molecular recognition.*

Chemistry

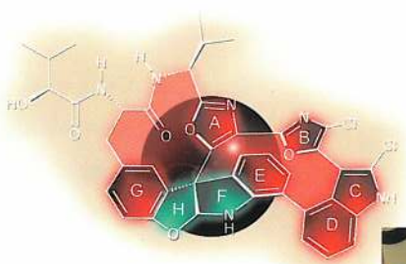
2002 DEPARTMENT HIGHLIGHTS

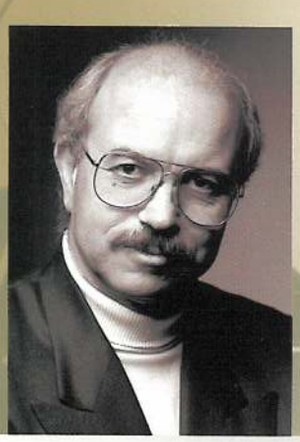
CHAIR K.C. NICOLAOU, PH.D., who is Aline W. and L.S. Skaggs Professor of Chemical Biology and Darlene Shiley Chair in Chemistry, was the 2002 winner of the Nobel Laureate Signature Award, with Phil Baran, a 2002 graduate of the TSRI Chemistry Program. Nicolaou also won the Tetrahedron Prize for Creativity in Organic Chemistry.

PROFESSOR ALBERT ESCHENMOSER, PH.D., won the Roger Adams Award in Organic Chemistry given for "outstanding contributions to research in organic chemistry defined in its broadest sense." Eschenmoser also received the Oparin Medal, the highest recognition of the International Society for the Study of the Origin of Life.

CHI-HUEY WONG, PH.D., Ernest W. Hahn Professor and Chair in Chemistry, was elected a member of the National Academy of Sciences.

DALE BOGER, PH.D., Richard and Alice Cramer Professor of Chemistry, received the 2002 Paul Janssen Prize for Creativity in Organic Synthesis.





CHAIR: **K.C. NICOLAOU, PH.D.** NUMBER OF PRINCIPAL INVESTIGATORS: **23** NUMBER OF OTHERS IN DEPARTMENT: **201**

MEMBERS OF THE DEPARTMENT OF CHEMISTRY INCLUDE (LEFT TO RIGHT) CHAIR K.C. NICOLAOU, PH.D., ASSOCIATE PROFESSOR ERIK SORENSEN, PH.D., PROFESSOR CHI-HUEY WONG, PH.D., PROFESSOR KIM JANDA, PH.D., AND PROFESSOR DALE BOGER, PH.D. ASSISTANT PROFESSOR FLOYD ROMESBERG, PH.D., USES A FEMTOSECOND LASER SPECTROMETER TO PROBE THE FLEXIBILITY OF PROTEINS. IN 2002, NICOLAOU SYNTHESIZED DIAZONAMIDE A, A PRODUCT WITH POTENT ANTITUMOR ACTIVITY.

PETER SCHULTZ, PH.D., professor and Scripps Family Chair, won the Paul Ehrlich & Ludwig Darmstaedter Award.

NICOLAOU, WONG, K. BARRY SHARPLESS, PH.D., (who is W.M. Keck Professor of Chemistry), BOGER, and JULIUS REBEK, PH.D., (who is professor and director of The Skaggs Institute for Chemical Biology) were included in the Institute of Scientific Information's list of "100 Most-Cited Researchers in Chemistry" for the period January 1992 through June 2002.

2002 RESEARCH HIGHLIGHTS

BOGER disclosed the first total synthesis of ramoplanin—a complex antibiotic. Ramoplanin inhibits cell wall biosynthesis in bacteria and is active against emerging antibiotic-resistant bacterial infections.

ASSOCIATE PROFESSOR M.G. FINN, PH.D., published the first reports of the use of icosahedral virus particles as building blocks for organic chemistry (with PROFESSOR J. JOHNSON, PH.D., Department of Molecular Biology). This work provides a bridge between the worlds of chemistry, which features known, but relatively small molecular structures, and biology, which features large entities of uncertain structure.

PROFESSOR KIM JANDA, PH.D., Ely R. Callaway, Jr., Chair in Chemistry, discovered that nornicotine, a nicotine metabolite and constituent of tobacco, can catalyze chemical reactions as well as modify proteins *in vivo*, implicating nornicotine in diabetes, cancer, aging, and arteriosclerosis.

Janda prepared the first human antibodies raised against *Bacillus* spores, in a species similar to that which causes anthrax. The study demonstrated spore detection and may lead to a new treatment for victims of anthrax.

Janda also showed that immunization with a synthetic glycoconjugate leads to up to 94 percent protection against septic shock, the tenth-leading cause of death in the United States today.

NICOLAOU synthesized Diazonamide A, a marine-derived natural product with potent antitumor activity. This feat provides a potential lead to new anticancer agents.

ASSISTANT PROFESSOR FLOYD ROMESBERG, PH.D., and his group, in collaboration with the Shultz group, developed several unnatural base pairs that are stable and replicated by polymerase enzymes. This is part of a broader effort to expand the information potential of DNA. Such unnatural bases pairs could, in principal, be used to expand an organism's genetic alphabet and encode proteins not found in nature.

The Romesberg group also recently developed a spectroscopic method to quantitatively characterize protein flexibility and folding. The lab is using this approach to understand molecular recognition in the immune system.

Using high-throughput screens, the group identified six novel proteins that function to maintain genome stability. The same techniques are being used to identify proteins required for cell mutation.

SHARPLESS, in collaboration with FINN, discovered an extremely potent non-covalent inhibitor of acetylcholinesterase using his "click chemistry" approach, where the enzyme itself recruits the building blocks and synthesizes the inhibitor in its active site.

Sharpless also discovered the copper(I)-catalyzed ligation of azides and terminal alkynes, one of the most selective and efficient catalytic processes known to date.

The laboratory of ASSOCIATE PROFESSOR ERIK SORENSEN, PH.D., achieved gram-scale laboratory syntheses of the structurally complex and potent microtubule-stabilizing natural product (–)-FR182877 and its enantiomer. This research led to the first report of tandem transannular Diels-Alder reactions and provided a chemical rationalization of the complex hexacyclic architecture of FR182877, a potent antitumor agent.

WONG developed saccharide microarrays in microtiter plates for high-throughput screen of saccharides and aminoglycosides targeting proteins and RNA associated with diseases.

Wong elucidated the mechanism of a sulfotransferase and discovered a potent and highly selective inhibitor. Sulfotransferases are involved in viral entry to hosts, cancer metastasis, thrombosis, and inflammatory reactions and are new targets for drug discovery. ■

MISSION *To understand how the immune system functions in health and disease, which includes infectious diseases, allergy, cancer, and autoimmune diseases. Each member of the department is committed to scientific excellence, to training young scientists, and to participating in professional organizations that insure the support of the highest quality science.*

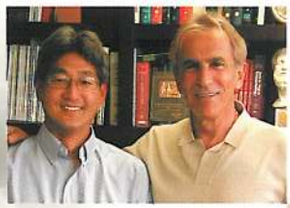
Immunology

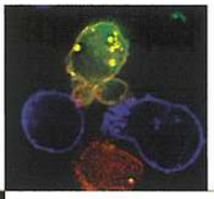
2002 DEPARTMENT HIGHLIGHTS

A number of IMMUNOLOGY FACULTY participate in the National Institutes of Health (NIH) grant review process. This activity helps support efforts of the broader scientific community, insures that NIH research dollars go to the best scientists, and reinforces the image of excellence that is the hallmark of TSRI's faculty. NIH REVIEW GROUP members include Professor Gary Bokoch, Ph.D., Professor David Cheresh, Ph.D., Professor Linda Curtiss, Ph.D., Associate Professor Ann Feeney, Ph.D., Associate Professor Wendy Havran, Ph.D., Associate Professor Jonathan Kaye, Ph.D., Associate Professor Dwight Kono, M.D., Associate Professor Nigel Mackman, Ph.D., Professor David Nemazee, Ph.D., Professor Nora Sarvetnick, Ph.D., Professor Linda Sherman, Ph.D., and Associate Professor Peter Tobias, Ph.D.

IMMUNOLOGY FACULTY hold key positions with consortiums or foundations focused on solving major heath problems worldwide. For example, PROFESSOR DENNIS BURTON, PH.D., directs the International AIDS Vaccine Initiative Neutralizing Antibody Consortium. PROFESSOR IAN WILSON, D.PHIL., is also a member. The consortium is investigating the interaction of broadly neutralizing antibodies with the virus at the molecular level in an effort to further the development of an HIV vaccine.

TSRI PROFESSOR ARGYRIOS THEOFILOPOULOS, M.D., was awarded an honorary doctorate of medicine from the University of Athens in Greece.





CHAIR: **RICHARD ULEVITCH, PH.D.** NUMBER OF INVESTIGATORS: **54** NUMBER OF OTHERS IN DEPARTMENT: **352**

MEMBERS OF THE DEPARTMENT OF IMMUNOLOGY INCLUDE (LEFT TO RIGHT) CHAIR RICHARD ULEVITCH, PH.D., ASSOCIATE PROFESSOR DWIGHT KONO, M.D., AND PROFESSOR ARGYRIOS THEOFILOPOULOS, M.D., PROFESSOR DENNIS BURTON, PH.D., AND ASSOCIATE PROFESSOR DAVID SCHLAEPFER, PH.D. THE DEPARTMENT'S WORK HAS IMPLICATIONS FOR THE DEVELOPMENT OF VACCINES AND THE UNDERSTANDING OF THE IMMUNE RESPONSE AT A MOLECULAR LEVEL, AMONG OTHER IMPORTANT TOPICS.

RESEARCH ASSOCIATE T. ZAL, PH.D., and his colleagues in the laboratory of ASSOCIATE PROFESSOR NICHOLAS GASCOIGNE, PH.D., are using real-time fluorescence resonance energy transfer (FRET) to study molecular interactions at the cell surface during T-lymphocyte activation. The use of biophysical techniques to measure real-time changes in living cells provides a new level of molecular detail about crucial processes in the immune response.

Additional studies of the structure of key molecules of the immune system at the molecular level are being undertaken by ASSOCIATE PROFESSOR LUC TEYTON, M.D., PH.D., and his collaborators, including long-standing collaborators in the Wilson laboratory.

Understanding the function of specific genes and defining genetic disposition to disease continues to be a major department focus. It involves the study of both B and T lymphocytes and is exemplified in the work of THEOFILOPOULOS and KONO. They have defined a paradigm of tumor immunotherapy involving T-cell homeostatic proliferation whereby a broad anti-tumor response is induced. This work, published in the *Journal of Clinical Investigation,* may lead to new approaches to tumor therapy.

The biochemical signals that lead to homeostatic proliferation and survival of naïve T cells have also been the subject of studies in the laboratory of ASSOCIATE PROFESSOR CHARLES SURH, PH.D. A recent study published in *Proceedings of the National Academy of Sciences* highlights a key role for cytokine IL-7 in this process.

The function of a unique subset of T cells in epithelial tissues are the subject of intense efforts in the HAVRAN laboratory. During the past year, this laboratory's newest findings have appeared in *Science* and in *Proceedings of the National Academy of Sciences,* documenting a key role for this T-cell subset in wound healing and providing new paradigms to study the immune system's role in this process.

NEMAZEE and colleagues demonstrated the role of receptor editing in B-cell development. Nemazee is recognized as having made the key observations that support the role of receptor editing in a number of processes related to B-cell development and function. A recent study in *Science* describes the contribution of receptor editing to the antibody repertoire.

THE DEPARTMENT OF IMMUNOLOGY continues to be recognized for its studies defining intracellular signaling pathways. Milestones from the past year include:

- Studies published in *Science* from the laboratory of ASSOCIATE PROFESSOR J. HAN, PH.D., that define an entirely new paradigm for MAP kinase activation not involving the classical upstream MAP kinases.
- A key role for a coagulation protein, Protein C, was established for the treatment of septic shock. Recent studies by ASSOCIATE PROFESSOR WOLFRAM RUF, M.D., and RESEARCH ASSOCIATE MATHIAS RIEWALD, M.D., appearing in *Science* document a key role for activated Protein C, its receptor on the surface of endothelial cells, and one of the Protease Activated Receptors (PAR1) in induction of anti-apoptotic and anti-inflammatory genes.
- Understanding cell migration at the molecular level is essential to controlling a number of human diseases, including malignancy and autoimmune disease. The laboratory of ASSOCIATE PROFESSOR DAVID SCHLAEPFER, PH.D., has approached this problem by investigating how focal adhesion kinase (FAK) integrates multiple extracellular signals to control cell migration. A publication in *Nature Cell Biology* highlights one of its most recent efforts, in which signals from growth factor receptors and integrins are shown to be mediated by FAK.
- Two studies by BOKOCH and his collaborators published in *Nature Cell Biology* provide a better understanding of the role of RAC and Cdc42, two low molecular weight GTP binding proteins, in regulating cell signaling to the actin cytoskeleton. These studies help define the complex process of cell movement at the molecular level. ■

MISSION *To understand the fundamental molecular events that underlie the processes of life.*

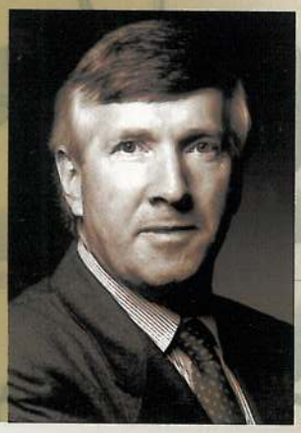
Molecular Biology

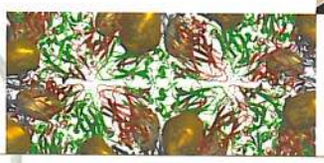
2002 DEPARTMENT HIGHLIGHTS

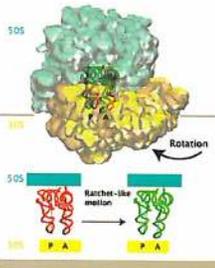
KURT WÜTHRICH, PH.D., Cecil H. and Ida M. Green Visiting Professor of Structural Biology and member of The Skaggs Institute for Chemical Biology, was awarded the 2002 Nobel Prize in Chemistry for applying the technique of nuclear magnetic resonance to solving the structure of biological macromolecules. (See interview, page 5.)

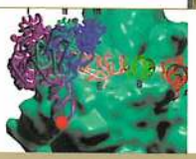
PROFESSOR CHARLES BROOKS, PH.D., and PROFESSOR DAVID CASE, PH.D., are part of a group of scientists from local research institutions who have been awarded $10.5 million over the next five years from the National Science Foundation to establish a leading center in the emerging field of theoretical biological physics, the Center for Theoretical Biological Physics. Biological physics encompasses such areas as spectroscopy and structural biology, which use the discoveries and the laws of physics to study problems in biology.

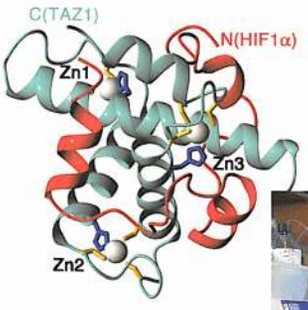
PROFESSOR IAN WILSON, D.PHIL., was elected to membership of the American Academy of Arts and Sciences, an honor that is the result of a highly competitive process recognizing those who have made preeminent contributions to a scholarly field or profession.

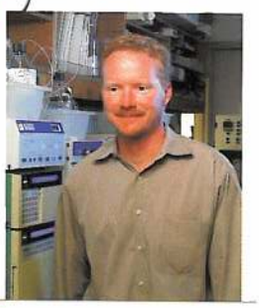












CHAIR: **PETER WRIGHT, PH.D.** NUMBER OF PRINCIPAL INVESTIGATORS: **59** NUMBER OF OTHERS: **357**

MEMBERS OF THE DEPARTMENT OF MOLECULAR BIOLOGY INCLUDE (LEFT TO RIGHT) CHAIR PETER WRIGHT, PH.D., PROFESSOR IAN WILSON, D.PHIL., AND PROFESSOR CARLOS BARBAS III, PH.D. HIGHLIGHTS FROM THE DEPARTMENT IN 2002 INCLUDE THE DEVELOPMENT OF A METHOD TO ATTACH MOLECULES TO THE SURFACE OF A VIRUS, THE ESTABLISHMENT OF A CENTER THAT WILL FURTHER THE UNDERSTANDING OF THE EMERGING FIELD OF BIOLOGICAL PHYSICS, AND THE SOLUTION OF THE STRUCTURE OF A PROTEIN ESSENTIAL FOR CANCER TUMOR GROWTH.

Assistant Professor Flavio Grynszpan, Ph.D., and Associate Professor Vito Quaranta, M.D., received seed funding from the California Breast Cancer Research Program to design breast cancer drugs. The scientists plan to use the $136,000 to develop inhibitors of proteins that belong to a family of enzymes, matrix metalloproteinases, known to be responsible for the invasive properties of breast cancer cells.

2002 RESEARCH HIGHLIGHTS

Professor Paul Russell, Ph.D., and Professor John Yates, Ph.D., (Department of Cell Biology) characterized an enzyme, Cid13, as playing a novel role in regulating the expression of a gene in fission yeast *Schizosacharomyces pombe.* The collaborators determined that the enzyme was involved in RNA metabolism. This finding may have implications for the treatment of cancer.

A team of researchers led by Peter Wright, Ph.D., professor, chair, and Cecil H. and Ida M. Green Investigator in Medical Research, and Jane Dyson, Ph.D., professor, solved the structure of a protein essential for cancer tumor growth. Blocking this protein, HIF-1, has already proven effective in stopping tumor growth.

Using a combination of chemistry and molecular genetics, Assistant Professor Tianwei Lin, Ph.D., Professor John Johnson, Ph.D., and colleagues found a way to attach a wide range of molecules to the surface of a virus, enhancing the virus with the properties of those molecules. Their technique may find applications in materials science, medicine, and molecular electronics. One possible application is to build circuits of conducting molecules on the surfaces of viruses and form a component of a molecular-scale computer.

A group of scientists led by Wright and Dyson solved the structure of a nuclear receptor activator and the general transcription coactivator, CBP, two critical human proteins that are normally unstructured in the cell, but fold synergistically so that together they form an active biological structure. The structures may lead to new therapies, since the proteins are important regulators of genes essential for development and reproduction and are implicated in cancer and other diseases.

Paul Schimmel, Ph.D., Ernest and Jean Hahn Professor and Chair of Molecular Biology and Chemistry, and Associate Professor Martin Friedlander, M.D., Ph.D., (Cell Biology) found that a naturally occurring protein, tryptophanyl-tRNA synthetase, is a potentially potent inhibitor of angiogenesis, the process whereby new blood vessels are formed from existing ones. Since abnormal angiogenesis is the leading cause of eye diseases such as age-related macular degeneration and diabetic retinopathy—affecting tens of millions in the United States—this finding may lead to important new therapies.

A team of chemists led by Carlos Barbas III, Ph.D., professor and Janet and W. Keith Kellogg II Chair in Molecular Biology, used novel aldehyde chemistry and the amino acid proline as a catalyst to selectively synthesize a number of compounds, including novel functionalized amino acids and derivatives. These compounds have the potential to be converted into antibiotics or unusual amino acids, which are common to HIV protease inhibitors.

A collaboration between Wilson and Chi-Huey Wong, Ph.D., (Chemistry) who is Ernest W. Hahn Professor and Chair in Chemistry, 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 (D-2-deoxyribose-5-phosphate aldolase) caught in the act of catalyzing a reaction on its substrate. This research should prove invaluable as a tool for drug synthesis.

Simultaneous reports by two TSRI teams, led by Russell, and Associate Professor Clare H. McGowan, Ph.D., identified the "resolvase" enzyme that may be responsible for generating genetic diversity during sexual reproduction. The discovery of the enzyme could lead to improved cancer chemotherapy. ■

MISSION *To have a meaningful impact on human health.*

Molecular & Experimental Medicine

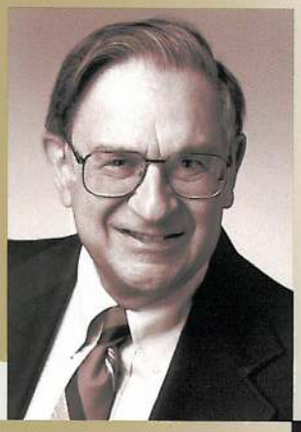
2002 DEPARTMENT HIGHLIGHTS

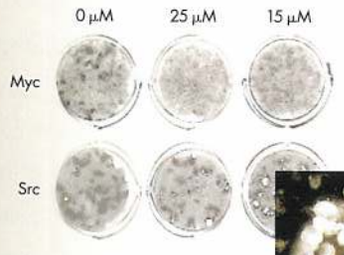
PROFESSOR FRANCIS CHISARI, M.D., was elected to membership in the National Academy of Sciences. Chisari joins Molecular and Experimental Medicine colleagues PROFESSOR BERNARD BABIOR, M.D., PH.D., CHAIR ERNEST BEUTLER, M.D., and PROFESSOR PETER VOGT, PH.D., as a recipient of this honor. Chisari was also elected to Fellowship in the American Academy of Microbiology in recognition of excellence, originality, and creativity in the microbiological sciences, joining fellow investigators PROFESSOR JAMES HOCH, PH.D., and PROFESSOR ENG TAN, M.D.

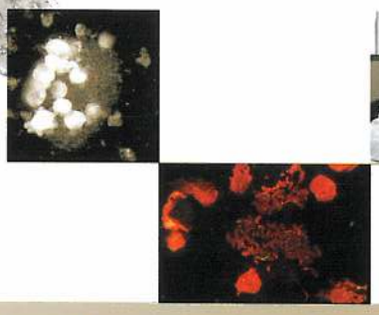
PROFESSOR ERIC F. JOHNSON, PH.D., won the 2002 Bernard B. Brodie Award in Drug Metabolism from the American Society for Pharmacology and Experimental Therapeutics for outstanding original research contributions in drug metabolism and disposition.

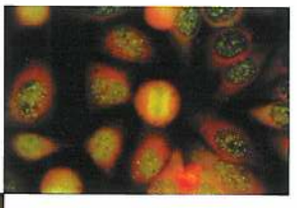
PROFESSOR ZAVERIO M. RUGGERI, M.D., received the Ercole Pisello Award from the Associazione Giuseppe Corradi in Bevagna, Italy. The prize honors an exceptional individual whose contributions are "of high relevance in the medical and scientific field."

PROFESSOR ENG TAN, M.D., was the recipient of the Western Society for Clinical Investigation's 2002 Mayo Soley Award, presented annually to an investigator in the Western United States who has made original and important contributions to research.

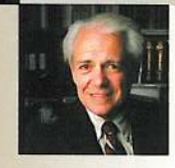








CHAIR: **ERNEST BEUTLER, M.D.** NUMBER OF INVESTIGATORS: **55** NUMBER OF OTHERS IN DEPARTMENT: **286**



MEMBERS OF THE DEPARTMENT OF MOLECULAR AND EXPERIMENTAL MEDICINE INCLUDE (LEFT TO RIGHT) CHAIR ERNEST BEUTLER, M.D., PROFESSOR FRANCIS CHISARI, M.D., AND PROFESSOR ZAVERIO RUGGERI, M.D. WORK IN THE DEPARTMENT INCLUDES AN EFFORT TO ISOLATE SMALL MOLECULE INHIBITORS OF MYC, A PROTEIN IMPORTANT IN HUMAN CANCERS, RESEARCH ON METASTATIC BREAST CANCER CELLS, AND INVESTIGATIONS OF AUTOIMMUNE DISEASES.

2002 RESEARCH HIGHLIGHTS

BIOCHEMISTRY

Division head: Professor Bernard Babior, M.D., Ph.D.

Professor Peter J. Sims, M.D., Ph.D., and Associate Professor Therese Wiedmer, Ph.D., focused on the biology of phospholipid scramblases, a family of proteins implicated in growth factor signaling. Aberrant expression may play a role in tumor formation and increased susceptibility to viral infection.

Associate Professor TakaoYagi, Ph.D., studied the mechanism of respiration that takes place in mitochondria, the powerhouses of living organisms. Dysfunction of respiration in mitochondria causes aging, neurodegenerative diseases (such as Parkinson's disease, amyotrophic lateral sclerosis), and cell death.

Babior's laboratory is studying oxygen metabolism in white blood cells. These cells manufacture reactive oxidants that they use to kill bacteria important for protection against infection.

The Johnson laboratory is directed toward understanding how the structural diversity and regulation of human P450 enzymes determine an individual's ability to avoid the adverse effects of exogenous chemicals.

Assistant Professor Xiaohua Wu, Ph.D., is determining the mechanisms underlying DNA damage repair and cell-cycle checkpoint control and addressing how genome stability is maintained, with the goal of providing insight into the molecular bases of diseases associated with genome instability and cancer.

CELLULAR BIOLOGY

Division head: Professor James Hoch, Ph.D.

Associate Professor Marta Perego, Ph.D., and Research Associate Lynn Hancock, Ph.D., individually mutated the genes for every two-component signal transduction system in pathogenic *Enterococcus faecalis* strains. They discovered the signaling systems that regulate biofilm persistence, antibiotic resistance, and structural stability of the bacterium.

Research Associate Haiyan Zhao, Ph.D., Associate Professor Kottayil Varughese, Ph.D., and Hoch added to our understanding of mechanisms of signaling by successfully obtaining a co-crystal of the Spo0A response regulator transcription factor with its DNA regulatory site. Spo0A controls anthrax toxin synthesis and other pathogenesis genes in *Bacillus anthracis* and may provide a target for the design of anti-anthrax agents.

EXPERIMENTAL HEMOSTASIS AND THROMBOSIS

Division head: Professor Zaverio Ruggeri, M.D.

Several studies are underway to improve understanding of the diseases that cause excessive blood loss or result in blood clots that occlude arteries and veins and cause heart attack, stroke, and emboli in the lungs.

Assistant Professor Brunhilde Felding-Haberman, Ph.D., is investigating how interactions of tumor cells with normal blood and vascular cells can favor the spreading of cancer. Other efforts by Associate Professor Daniel Salomon, M.D., and colleagues have been directed toward demonstrating the risks of the transplantation of animal organs into humans.

EXPERIMENTAL PATHOLOGY

Division head: Professor Francis Chisari, M.D.

Chisari's group demonstrated that interferon inhibits hepatitis B virus replication by activating an enzyme system in the infected cells that usually degrades misfolded cellular proteins. The team also found that interleukin-18 and activated macrophages inhibit hepatitis B virus replication. In collaboration with the Schultz lab, the Chisari group also identified the cellular genes likely to mediate the immune response for control of hepatitis B virus (HBV) and hepatitis C infections.

Assistant Professor Luca G. Guidotti, D.V.M., Ph.D., investigated the immunopathological mechanisms responsible for liver damage during HBV infection. Using HBV transgenic mice, the laboratory studied how antigen non-specific inflam-

(Continued on next page)

matory cells are recruited into the liver by chemokines and other factors and how these cells enhance the liver disease initiated by antigen-specific cytotoxic T lymphocytes.

HEMATOLOGY

Division head: CHAIR ERNEST BEUTLER, M.D.

BEUTLER'S laboratory completed the largest-ever DNA-based population study (41,000 samples) in collaboration with Kaiser Permanente Hospital in San Diego of mutations causing hemochromatosis—a metabolic disorder in which excess deposits of iron occur in the liver, pancreas, and other organs. Surprisingly, even people who are homozygous for the mutation that causes hemochromatosis rarely manifest the disease. These findings may lead to a reassessment of widespread screening.

The laboratory of ASSOCIATE PROFESSOR ROBERTA GOTTLIEB, M.D., showed that much of the damage produced in heart attacks is due to the activity of a family of enzymes known as cytochrome P450 mono-oxygenases, or CYP enzymes, which can produce excessive amounts of reactive oxygen species during reperfusion. In models, the lab showed that inhibition of CYP enzymes after the occlusion of a blood vessel could substantially reduce the severity of a heart attack. This approach holds promise for humans.

ONCOVIROLOGY

Division head: PROFESSOR PETER VOGT, PH.D.

The VOGT laboratory, in collaboration with the laboratory of PROFESSOR DALE BOGER, PH.D., (Chemistry) isolated small molecule inhibitors of the Myc oncoprotein, which is causally involved in numerous human cancers and functions by binding to a partner protein, Max. These small molecule inhibitors inhibit the interaction of Myc with its obligatory partner Max and thus interfere with tumor-producing activity.

The laboratory of ASSOCIATE PROFESSOR DONG-ER ZHANG, PH.D., has discovered the first protease (UBP43) involved in the regulation of protein ISG15 modification. Protein ISG15 conjugation is strongly increased upon viral and bacterial infection.

RHEUMATOLOGY

Division head: PROFESSOR JOEL BUXBAUM, M.D.

TAN continued to extend his analyses of autoantibodies from inflammatory to malignant disease, demonstrating an increase in both the frequency and specificity of autoantibodies in certain types of malignancies and suggesting that such analyses might be useful in cancer diagnosis.

ASSISTANT PROFESSOR ZHIXING PAN, M.D., PH.D., ASSOCIATE PROFESSOR MICHAEL ROBERTSON, PH.D., and ASSOCIATE PROFESSOR BRUCE ZURAW, M.D., collaboratively and individually identified interactions between ligands and their receptors and the subsequent signaling pathways involved in specific inflammatory and allergic responses.

ASSOCIATE PROFESSOR MICHAEL POLLARD, PH.D., in collaboration with ASSOCIATE PROFESSOR D.H. KONO, PH.D., (Immunology) and investigator Per Hultman (Linkoping University, Sweden), used models lacking a gene with a known function in the immune-inflammatory pathway to show the requirement for particular genes in generating an autoimmune response to an environmental agent—in this case mercury.

BUXBAUM and collaborators in Portugal showed that, in a disorder dependent on a mutation in a single gene that produces a dysfunctional protein, the age of onset of the disease may depend upon the interaction of a number of other apparently normal genes unlinked to the gene carrying the primary mutation. ■

MISSION *To define the cellular and molecular mechanisms responsible for the development and function of the nervous system.*

Neurobiology

2002 DEPARTMENT HIGHLIGHTS

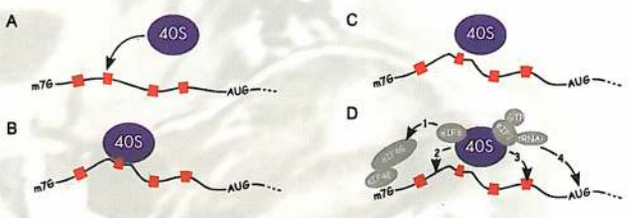
GERALD EDELMAN, M.D., PH.D., was awarded La Medaille de la Ville de Paris in Paris, France.

2002 RESEARCH HIGHLIGHTS

ASSOCIATE PROFESSOR VINCENT P. MAURO, PH.D., and EDELMAN formulated a new hypothesis regarding the control of protein translation in the cell. This so-called Ribosome Filter Hypothesis suggests that ribosomes themselves can act as regulatory elements, i.e. can actively recruit and selectively translate particular messages in the cell via interactions with messenger RNA. The idea has important consequences for understanding the control of developmental processes and aberrant protein production in disease states, as well as for use in overproduction of proteins for therapeutic uses. ASSOCIATE PROFESSOR KATHRYN L. CROSSIN, PH.D., together with colleagues in the department and at The Neurosciences Institute, identified conditions for culturing neural stem cells that generated neurons that formed networks and fired spontaneous action potentials. This was the first observation of stem cells from the embryonic brain forming physiologically functional neurons that assembled into appropriate networks. The work is significant for understanding the requirements for generating functional neurons from stem cells for cellular therapies.

GUEST SCIENTIST GEOFFREY OWENS, PH.D., designed an improved retroviral vector that could infect embryonic neural progenitor cells and sustain expression of a transgene, even after the cells differentiated into neurons and glia. Such vectors, which promote significant protein expression in multiple phases of cellular differentiation, are essential for successful gene therapy.

ASSISTANT PROFESSOR PETER W. VANDERKLISH, PH.D., demonstrated that the activation of metabotropic glutamate receptors causes spine elongation in the dendrites of hippocampal cells. Spines are the sites of synapse formation in these neurons and spine shape is important for proper neuronal functioning. His work also showed that a neurotrophic factor, BDNF, increased the expression of a cytoskeletal protein critical for synapse morphology. Together the studies help to link alterations in synapse formation and morphology with molecules known to be critical for learning and memory. ■



CHAIR: **GERALD EDELMAN, M.D., PH.D.** NUMBER OF PRINCIPAL INVESTIGATORS: **6** NUMBER OF OTHERS IN DEPARTMENT: **21**

CHAIR GERALD EDELMAN (ABOVE RIGHT) IS THE WINNER OF THE 1972 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE. ASSISTANT PROFESSOR PETER VANDERKLISH, PH.D., (RIGHT) IS SHOWN HERE WITH A MEMBER OF HIS LAB. IN 2002, ASSOCIATE PROFESSOR VINCENT MAURO, PH.D., AND EDELMAN FORMULATED THE RIBOSOME FILTER HYPOTHESIS, A NEW WAY OF LOOKING AT THE CONTROL OF PROTEIN TRANSLATION IN THE CELL.

MISSION *To focus on the mechanisms by which infectious, environmental, and inheritable agents lead to psychiatric, neurologic, or endocrine disorders of the brain, in order to acquire the information needed to devise novel treatments or effective prevention strategies. The department's research is built around five major clusters, with substantial cross-cluster collaboration: molecular, cellular, and systems neuropharmacology; neurovirology; neuro-immunology; psychopharmacology; and clinical neuro-psychopharmacology.*

Neuropharmacology

2002 DEPARTMENT HIGHLIGHTS

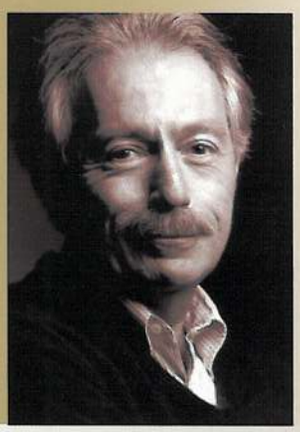
CHAIR FLOYD BLOOM, PH.D., became president of the American Association for the Advancement of Science, the world's largest general scientific society and publisher of the journal *Science.*

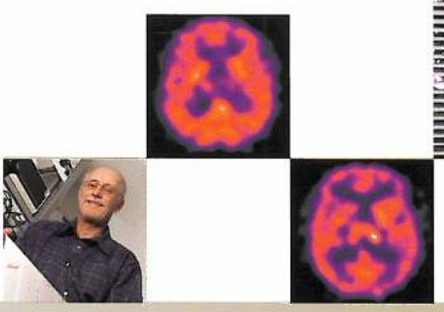
PROFESSOR GEORGE F. KOOB, PH.D., was awarded the Distinguished Research Award by the Research Society on Alcoholism.

ASSOCIATE PROFESSOR HOWARD FOX, M.D., PH.D., became chairman of the AIDS Neuropathogenesis and Comorbidity Factors NIH Study Section.

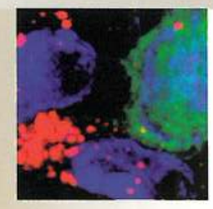
2002 RESEARCH HIGHLIGHTS

TAMAS BARTFAI, PH.D., professor and director of the Harold L. Dorris Neurological Research Center, and colleagues from the United Kingdom and Switzerland, described the first effective treatment for human serum amyloidosis, potentially applicable for treating Alzheimer's disease and amyloid disorders, and synthesized the first systemically active galanin agonists, showing that they represent a new class of anticonvulsant agents in the brain.





CHAIR: **FLOYD BLOOM, PH.D.** NUMBER OF INVESTIGATORS: **36** NUMBER OF OTHERS IN DEPARTMENT: **222**



MEMBERS OF THE DEPARTMENT OF NEUROPHARMACOLOGY INCLUDE (LEFT TO RIGHT) CHAIR FLOYD BLOOM, PH.D., PROFESSOR GEORGE ROBERT SIGGINS, PH.D., AND PROFESSOR GEORGE KOOB, PH.D. WORK IN THE DEPARTMENT HAS IMPLICATIONS FOR INFLAMMATORY DISEASES, SUCH AS DIABETES AND MULTIPLE SCLEROSIS, SLEEP DISORDERS, AND AIDS DEMENTIA, AMONG OTHER CONDITIONS AFFECTING THE CENTRAL NERVOUS SYSTEM.

Professor Michael Buchmeier, Ph.D., demonstrated a central role of chemokines, particularly IP-10 and RANTES, in the pathogenesis of central nervous system demyelination in a viral model, and mapped the induction of specific host response cytokine and chemokine genes on the murine coronavirus genome.

Associate Professor Iain L. Campbell, Ph.D., established a primary link between inflammation in the brain during development, activation of the sonic hedgehog-signaling pathway in granule neurons and the development of medulloblastoma—the most common malignant brain tumor in children.

Associate Professor Juan C. de la Torre, Ph.D., rescued for the first time a recombinant Arenavirus using reverse genetic approaches, and provided the first comprehensive analysis of changes in global gene expression in brains persistently infected with Borna disease virus, a novel neurotropic infectious agent causing neurodevelopmental and behavioral abnormalities.

Associate Professor Cindy Ehlers, Ph.D., identified the leading biological factors underlying the cause of alcoholism in Native American Mission Indians. Alcoholism occurs in more than 60 percent of this population.

Fox extended investigations into the causes of dementia, a devastating sequela of HIV infection, reporting that even quite early after infection, a significant increase of activated immune cells is present in the brain, and that this increase is indeed correlated with neurological dysfunction.

Associate Professor Donna Gruol, Ph.D., demonstrated that interleukin-6, a cytokine induced in the brain in injury and disease, causes neuroadaptive changes in developing neurons that are mediated by gene expression and result in altered neuronal physiology, potentially associated with fetal infection, perinatal asphyxia, and traumatic brain injury.

Associate Professor Steven J. Henriksen, Ph.D., reported a novel mechanism of brain attention and arousal based on neurophysiological studies of brainstem GABA containing projection neurons, a new neural systems substrate potentially affected in attention deficit disorder and schizophrenia.

Koob conceptualized an innovative process of long-term adaptive physiological regulation, termed allostasis, responsible for underlying psychopathology of drug addiction. He also established that reward deficit is a mechanism for the transition of drug use to drug addiction.

Professor Merrill M. Mitler, Ph.D., organized and supported an international cooperative study to establish norms for the Maintenance of Wakefulness Test (MWT), now a global medical resource, and collated and reviewed the literature on pharmacotherapy for narcolepsy.

Professor Michael B.A. Oldstone, M.D., provided the primary observation of the immune synapse *in vivo* and mapped molecules inside and outside the synapse important in the function of T cells engaging virus-infected cells. This data will be important for evaluating the efficacy of therapeutic interventions to control inflammatory diseases, optimizing vaccination strategies and assessing the efficiency of immune responses against tumors.

Associate Professor John Polich, Ph.D., developed a reliable paradigm using sensory-evoked brain potentials to quantify attention-focusing capabilities of the frontal lobes, useful to detect those at risk for alcoholism and those suffering from Parkinson's.

Professor George Robert Siggins, Ph.D., substantiated his hypothesis that metabotropic glutamate receptor activation regulates the sensitivity to ethanol of GABAergic and glutamatergic central synapses and demonstrated that ethanol increases GABAergic inhibitory neurotransmission by a novel presynaptic mechanism in virtually all neurons of the central amygdala.

Associate Professor Bert Weiss, Ph.D., showed that stress and exposure to drug-associated environmental cues interact to exacerbate relapse risk, and that this effect results from concurrent activation of receptors for the stress-regulatory neuropeptide, CRF, and endogenous opioid receptors.

Professor Lindsay Whitton, M.D., Ph.D., continued studies on the molecular and immune mechanisms involved in viral pathogenesis and antiviral immunity. ■

MISSION *To relieve human suffering by moving basic research to applications in medicine.*

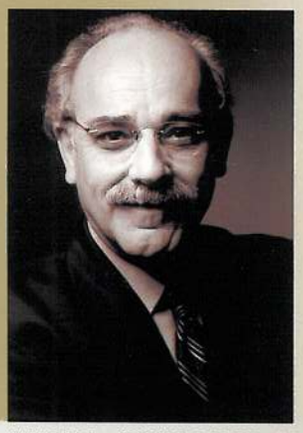
The Skaggs Institute for Chemical Biology

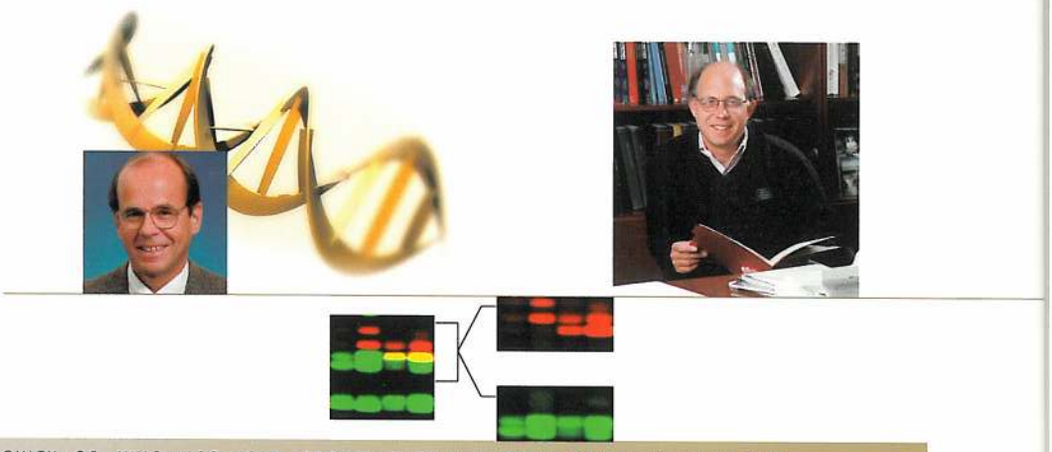
2002 HIGHLIGHTS

KURT WÜTHRICH, PH.D., Cecil H. and Ida M. Green Visiting Professor of Structural Biology, shared the 2002 Nobel Prize in Chemistry for the determination of protein structures in solution. (See interview, page 5.) This follows close on the heels of another Nobel Prize, the 2001 Nobel Prize in Chemistry, awarded to Skaggs Institute investigator K. Barry Sharpless, Ph.D., who is W.M. Keck Professor of Chemistry.

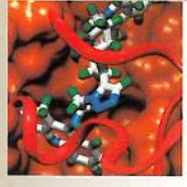
Numerous other prestigious honors were bestowed on Skaggs Institute faculty, including PROFESSOR ALBERT ESCHENMOSER, PH.D., who won the Oparin Medal and the Roger Adams Award in Organic Chemistry; PROFESSOR IAN WILSON, D. PHIL., who was elected to the American Academy of Arts and Sciences; DIRECTOR AND PROFESSOR JULIUS REBEK, PH.D., who won the American Institute of Chemists Chemical Pioneer Award; K.C. NICOLAOU, PH.D., (Aline W. and L.S. Skaggs Professor of Chemical Biology and Darlene Shiley Chair in Chemistry) who was selected to receive the Tetrahedron Prize; CHI-HUEY WONG, PH.D., (Ernest W. Hahn Professor and Chair in Chemistry), who was elected to the National Academy of Sciences; and DALE BOGER, PH.D., (Richard and Alice Cramer Professor of Chemistry) who received the Paul Janssen Award for Creativity in Organic Synthesis.

More than 300 publications were generated by Skaggs researchers in the past year.





DIRECTOR: **JULIUS REBEK, PH.D.** NUMBER OF FACULTY: **31**, WHO ALSO HOLD APPOINTMENTS WITH OTHER DEPARTMENTS AT TSRI. NUMBER OF OTHERS: **100** POSTDOCS AND **50** GRADUATE STUDENTS FUNDED BY THE INSTITUTE.



MEMBERS OF THE SKAGGS INSTITUTE FOR CHEMICAL BIOLOGY INCLUDE (LEFT TO RIGHT) DIRECTOR JULIUS REBEK, PH.D., PROFESSOR K. BARRY SHARPLESS, PH.D, WHO WON THE 2001 NOBEL PRIZE IN CHEMISTRY, AND PROFESSOR PETER SCHULTZ, PH.D. MORE THAN 300 PUBLICATIONS WERE GENERATED BY SKAGGS RESEARCHERS IN 2002, INCLUDING A PAPER BY SHARPLESS AND COLLEAGUES THAT SHOWED THE CREATION OF THE MOST POTENT BLOCKING AGENT KNOWN AGAINST AN ENZYME IMPLICATED IN ALZHEIMER'S DISEASE USING A NEW GENERAL STRATEGY FOR DRUG DISCOVERY. OTHER SKAGGS RESEARCHERS ARE DIRECTING THEIR EFFORTS AT ILLUMINATING THE HUMAN PROTEOME, THE MILLIONS OF POSSIBLE PROTEIN FORMS AND STATES IN THE CELL.

Synthesis lies at the heart of organic chemistry and the synthesis of natural products drives the discoveries of chemical biology. The flow of synthetic molecules from the Skaggs chemistry team at TSRI—NICOLAOU, BOGER, ASSOCIATE PROFESSOR ERIK SORENSEN, and SHARPLESS—has resulted in several remarkably active agents. During the past year antibiotic agents targeting cancer have been the focus of research: duocarmycins that strike at cancerous DNA; designed agents that inhibit growth of blood vessels to tumors; synthetic structures that stabilize microtubules reversibly and those that target proteins and nucleic acids irreversibly. Modified epithilones with reduced toxicity have been synthesized, and an inhibitor of acetyl cholinesterase with unprecedented affinity was created by a process in which the enzyme itself assembles the agent by selecting its components in the active site. The reagents "click" together in the space provided by the enzyme.

The discovery of the group led by TSRI PRESIDENT RICHARD LERNER, M.D., who is Lita Annenberg Hazen Professor of Immunochemistry and Cecil H. and Ida M. Green Chair in Chemistry, that antibodies are capable of destroying antigens by chemical methods is a profound one and likely to make its greatest impact in future years. It points to the versatility of the immune system and shows that radical new departures can be found in basic science. Current research is directed at identifying which of the activated forms of oxygen, i.e. ozone or hydroxyl radical, is responsible for the chemistry that protects the system from toxic agents.

A discovery that has deep significance for biology emerged from the work of PAUL SCHIMMEL, PH.D., Ernest and Jean Hahn Professor and Chair of Molecular Biology and Chemistry, and PETER SCHULTZ, PH.D., Professor and Scripps Family Chair, who have been manipulating the genetic code with the aim of engineering living organisms. This has resulted in the discovery of a molecule that inhibits angiogenesis and may also be able to target tumors. This shows such promise that a consortium of scientists were able to obtain long-term support from the National Institutes of Health to pursue the findings.

The group led by JEFFERY KELLY, PH.D., who is Lita Annenberg Hazen Professor of Chemistry, promises to bring a medicinal chemistry effort at TSRI one step closer to clinical trials. This project involves the misfolding of proteins implicated in debilitating diseases such as Alzheimer's and other amyloidoses. The researchers found that a non-steroidal, anti-inflammatory drug approved for other indications prevented this misfolding. The drug is available orally and the results of human clinical studies have been so impressive that it, or a second-generation analog, will be effective in a greater patient population.

A group led by REBEK demonstrated that it could achieve chemical amplification (speeding up a reaction as it proceeds) without the presence of an autocatalyst (a product of the reaction that acts as a catalyst for more product). The findings show a different way of turning a reaction on and off. These findings are important to the study of the dynamics of living systems. ■

MISSION *To prepare students to meet the scientific challenges of the next century in an environment tailored to accommodate individual interests and capabilities.*

The Kellogg School of Science and Technology

2002 HIGHLIGHTS

TSRI named its graduate college "Kellogg School of Science and Technology" in honor of the extraordinary contributions to science and education of philanthropists JANET R. ("JEAN") KELLOGG and W. KEITH KELLOGG II. Their support of the program brings together two long-standing objectives in their giving—support for science and support for education. In special recognition, TSRI conferred honorary doctorates of science on the Kelloggs at its 2002 commencement ceremony.

An April 2002 edition of *U.S. News & World Report* ranked TSRI's graduate program sixth overall in chemistry—and second in the specialty of organic chemistry—among all such programs in the nation. The publication also ranked TSRI's Ph.D. program ninth overall in the biological sciences, and sixteenth in the specialty of biochemistry.

DEAN: **JEFFERY KELLY, PH.D.** ASSOCIATE DEANS: **JAMES WILLIAMSON, PH.D., STEPHEN MAYFIELD, PH.D.**

PROFESSOR JEFFERY KELLY, PH.D., (LEFT) IS DEAN OF THE KELLOGG SCHOOL OF SCIENCE AND TECHNOLOGY, NAMED IN HONOR OF JANET R. AND W. KEITH KELLOGG II (TOP) IN 2002. OTHER IMAGES SHOW (FOREGROUND, LEFT TO RIGHT) 2002 COMMENCEMENT SPEAKER TSRI PROFESSOR PAUL SCHIMMEL, PH.D., THE ANNUAL RETREAT FOR STUDENTS AND FACULTY, TSRI'S TENTH COMMENCEMENT CEREMONY AND NEW STUDENTS IN THE PROGRAM.

TSRI students were recognized by a number of prestigious awards. PHIL BARAN, PH.D., a 2002 graduate of the program, and his advisor K.C. NICOLAOU, PH.D., who is department chair, Aline W. and L.S. Skaggs Professor of Chemical Biology, and Darlene Shiley Chair in Chemistry, won the American Chemical Society's 2002 Nobel Laureate Signature Award. This honor recognizes the achievements of both an outstanding graduate student and his/her mentor. Others students in the Kellogg School received fellowships from the American Heart Association; the Howard Hughes Medical Institute; the National Science Foundation; the National Institutes of Health; the National Defense and Science Engineering Graduate Fellowship Program; Achievement Rewards for College Scientists; the American Chemical Society; La Jolla Interfaces in Science; the National Science and Engineering Research Council of Canada; and several private donors.

Twenty-one students graduated in May in a commencement ceremony featuring TSRI PROFESSOR PAUL SCHIMMEL, PH.D., who is Ernest and Jean Hahn Professor and Chair of Molecular Biology and Chemistry, as the keynote speaker. Some of this year's graduating students now work at Harvard University, Massachusetts Institute of Technology, Uppsala University (Sweden), University of Minnesota, University of California at San Diego, the Genomics Institute of the Novartis Research Foundation, Pharmacia Corporation, and Attenuon, L.L.C.

Thirty-six students entered the program. Students follow a core curriculum in either macromolecular and cellular structure and chemistry (MCSC) or chemistry, in addition to enrolling in elective courses. Elective courses provide training in such areas as x-ray diffraction, statistical mechanics, special nuclear magnetic resonance techniques, immunology, neurosciences, and virology. Classes are offered by more than 100 faculty members representing every department at TSRI.

The Kellogg School launched a new web site—at http://www.scripps.edu/phd/i_flashhome.html—which reflects the high quality of the graduate programs. The new site offers a contemporary look, easy navigation, and up-to-date information. In addition to welcome letters from the president, the dean, and the associate deans, the site features descriptions of faculty research, pictures of the campus, and links to related information, including news, lectures, and student resources.

Eighteen graduate students served as mentors to high school students through TSRI's Summer Research Education Program, which was created to expose the high school students to a variety of contemporary issues in basic biomedical research, provide a hands-on laboratory experience, and motivate and prepare students for continuing education in the sciences. Graduate students also developed and presented two series of tutorials—one for local high school students and another for middle and high school science teachers. ■

Dear Friends,

The year 2002 marks another remarkable milestone for The Scripps Research Institute. For the second year in a row, a Scripps scientist has been awarded the Nobel Prize in Chemistry. Dr. Kurt Wüthrich is Cecil H. and Ida M. Green Visiting Professor and a member of The Skaggs Institute for Chemical Biology. Dr. Wüthrich was lauded by the Nobel Committee for his work in nuclear magnetic resonance spectroscopy (NMR), which reveals the three-dimensional structure of many proteins.

The following pages reflect the names of those who have donated gifts supporting biomedical research through the work of our scientists in 2002, as well as names of individuals who have informed us they have included TSRI in their estate plans.

We are sincerely grateful for all the support of basic research we have received this year at TSRI. Private support is critical to our work in order to pursue new and exciting research opportunities and initiatives. Private philanthropy plays a pivotal role ensuring the continuation of uninterrupted support of mainstream research. Every major scientific breakthrough emerges from an untested idea—your support has made possible the extraordinary breakthroughs the scientists at TSRI have accomplished as noted in this edition of *Endeavor's* Year in Review.

In spite of an uncertain world, the importance of charitable giving remains constant. With your continued support, The Scripps Research Institute will remain a leader in the scientific community, while making a difference in the lives of individuals. The outlook for a brighter future and quality of life for each of us is held in the developments centered around the scientific investigations of today.

We shall always view our support from you as a critically important partnership in the search for ameliorating the devastation of disease.

In appreciation,

Deeda Blair

Deeda Blair
Chair of the Development Committee
TSRI Board of Trustees

Private philanthropy has made a tremendous impact on TSRI's ability to stay at the forefront of research that will provide the cures of tomorrow. On the following pages we recognize those who have contributed to our success this year. We give special recognition to some of the people and organizations who have shown how private philanthropy carries forward the work of TSRI's programs and scientists.

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
Gordon M. Anderson Charitable Lead Trust
Anonymous (17)
Arthritis Foundation
Donald E. and Delia B. Baxter 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
Cytel Corporation
Damon Runyon-Walter Winchell
Cancer Fund
Harold L. Dorris Neuroscience Foundation
Helen L. Dorris Foundation
Ellison Medical 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
Theodore Hart
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
Mr. and Mrs. Dirk C. Kok, Jr.
Leta Kramer
Leukemia and Lymphoma Society, Inc.
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.
Mr. Melvin S. Reeves
Fannie E. Rippel Foundation
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, 2001 to September 30, 2002

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 Heart Association
Anonymous (1)
Arthritis Foundation
Donald E. and Delia B. Baxter Foundation
The Arnold and Mabel Beckman Foundation
Cancer Research Institute, Inc.
Charles A. Dana Foundation
Damon Runyon-Walter Winchell
Cancer Fund
Harold L. Dorris Neuroscience Foundation
Ellison Medical Foundation
Mrs. Eugenia C. Glow
Mr. and Mrs. Bruce R. Hazard
Lita Annenberg Hazen Foundation
Howard Hughes Medical Institute
International AIDS Vaccine Initiative
Juvenile Diabetes Research Foundation
Mr. and Mrs. Dirk C. Kok, Jr.
The Koshland Foundation
Leukemia and Lymphoma Society, Inc.
Mr. and Mrs. Arthur R. Lindburg
G. Harold and Leila Y. Mathers Foundation
Mericos Eye Institute
National Foundation for Cancer Research
The James B. Pendleton Charitable Trust
Fannie E. Rippel Foundation

$50,000–$99,999

American Diabetes Association
American Parkinson Disease Association
Anonymous (1)
ARCS Foundation, Inc.
William and Sharon Bauce Family Foundation

Graduate Program | W. Keith and Janet (Jean) Kellogg had two objectives when they gave to TSRI—support science and education. They have been long-standing philanthropists in these areas across the country and continue to leave this legacy in a permanent way at TSRI. The Kellogg School of Science and Technology is a gift that will support generations of scholars and scientists of the future.

The Charles C. and Sue K. Edwards Foundation
Frances Houlton
Susan G. Komen Breast Cancer Foundation
March of Dimes Birth Defects Foundation
Armstrong McDonald Foundation
Miramar & Company
Mr. Robert P. Scripps, Sr.
Allan and Anita Sutton

$25,000–$49,999

Anonymous (1)
The Blasker-Rose-Miah Fund
Boehringer Ingelheim, Ltd.
Elizabeth Glaser Pediatric AIDS Foundation
Max Kade Foundation, Inc.
Life Science Research Foundation
Myasthenia Gravis Foundation, Inc.
Rett Syndrome Research Foundation
W.E. Walker Foundation

$10,000–$24,999

American Chemical Society
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Tradition | Sam and Aline Skaggs have a long history in the tradition of philanthropy. The Skaggs became active in their association with the Institute in 1986. Ten years later they gave one of America's largest philanthropic gifts of $100 million over a 10-year period to create The Skaggs Institute of Chemical Biology, which has emerged as a driving force in rational drug design. As a family they have maintained a steady tradition of support that will affect all future generations.

Legacy | Since 1924, the Scripps family name has been synonymous with La Jolla, CA. Today we are still benefiting from Ellen Browning Scripps' first vision of a better quality of life through science. Robert, Charles, and Samuel Scripps continue to carry on the support of Miss Ellen's legacy. Their commitment to basic biomedical research has allowed scientists to pursue their full potential at the vital intersection of biology and chemistry and in five other critical areas. This legacy continues today in support of TSRI's mission.

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In Memoriam | Arthur Hill—He was a businessman, writer, and philanthropist with a great passion for life. Arthur and his wife, Julie, have been closely associated with TSRI since 1989. In 1990 he became patient #66 in the 2CdA clinical trials in fighting a disease called Hairy Cell Leukemia. Arthur supported us by writing many articles about science for our publications. His intellect, gentleness, and spirit of generosity is still felt at TSRI. Walter Fitch III—Over the past 20 years, Walter gave millions of dollars to many institutions in this community. Walter had long been associated with TSRI, having an understanding of the value of science. His constant giving of time and financial support was invaluable.

Innovation | Philanthropic gifts come packaged in many different forms. Evidence of this can be seen and appreciated on the campus of TSRI when people encounter the several innovative works of internationally acclaimed sculptor and TSRI board member John Safer. John's works stand in museums, galleries, universities, and embassies throughout the world. His most recent gift of sculpture to TSRI, *Flame of Knowledge*, was placed in memory of Norton Gilula, Ph.D.— the first dean of TSRI's Graduate School.

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Commitment | In 1984, Donald and Marilyn Short established an endowment to support basic research into the autoimmune disease lupus. Over the years, they have committed their personal support to furthering the endeavors of basic biomedical science at TSRI. Mr. and Mrs. Short have made an investment in the future knowing that their generosity and foresight will benefit not only their grandchildren and great-grandchildren but all of humanity.

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Community Spirit | There are organizations in our community that have shown time and time again their contribution to the richness of the San Diego community. The Wells Fargo Bank and The San Diego Foundation are two organizations that epitomize community spirit in their efforts to catalyze and nurture community projects such as TSRI's educational outreach programs. The Wells Fargo Foundation has been an important partner for many years through the Samuel H. French III and Katherine Weaver French Fund and the Maurice J. Masserini Charitable Trust through its support of TSRI's Summer Research Internship Program for teachers and middle and high school students. The San Diego Foundation, through its Blasker Grants Program, has funded several high school and undergraduate students to participate in the internship program in 2003. These community partners play an important role in ensuring the success of TSRI in training the next generation of scientists and perpetuating scientific knowledge.

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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 at a disadvantage in competing for grants. Their search for funds can 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 Building

In 1961, the Department of Experimental Pathology was the cornerstone of the newly established Scripps Clinic and Research Foundation (SCRF). With the arrival of Dr. Frank Dixon Jr., this department began investigations in the fledgling field of immunology that would be the genesis of The Scripps Research Institute (TSRI).

In just a few decades, TSRI has become one of the preeminent leaders in the field of immunology. The scope of study has grown dramatically to include groundbreaking investigations into diseases affecting millions of people worldwide. Diseases such as diabetes, cancer, AIDS, septic shock, Ebola infections, arthritis, lupus, multiple sclerosis, tuberculosis, hepatitis C, prion disease, and blood disorders are but a few that come under the scientific investigation of the one of the largest immunology research departments in the world. At the same time, the department has expanded its work into early clinical development, giving TSRI scientists an even greater opportunity to aid patients directly.

TSRI has a one-time opportunity to purchase the building that houses the Immunology department at a price below current market value. Raising a minimum of $16 million in private funds would enable the institute to commit to the purchase by the deadline of June 2003 and take advantage of this exceptional option. The building, which has been leased by TSRI since 1980, is the southern anchor to the main TSRI campus and houses TSRI's oldest and largest department, the Department of Immunology. Since 1980, the Immunology Building has been home to world leaders in unlocking the secrets of the complex human immune system and in developing potential treatments for various global killers.

A naming gift will assure a donor a high level of recognition in the world of biomedical science.

Giving Opportunities | Gifts of all sizes are welcome. Naming opportunities are available as follows:

Building	$ 5,000,000
South Campus	$ 3,000,000
Second Floor	$ 1,000,000
Third Floor	$ 1,000,000
Plaza Area	$ 500,000
Atrium/Gallery	$ 250,000
Large Conference Room	$ 200,000
Small Conference Room	$ 100,000
Laboratory	$ 75,000

Institute for Childhood and Neglected Diseases

The Institute for Childhood and Neglected Diseases at TSRI 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 $75,000 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 inter-disciplinary team of scientists to focus on understanding neuropathology in children and adolescents.

Giving Opportunities | Gifts of all sizes are welcome. 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 $75,000 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 will be enjoyed by successive generations of family members.

Giving Opportunities | Gifts of all sizes are welcome. 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 | Gifts of all sizes are welcome. 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 dedicated 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 | Gifts of all sizes are welcome. A gift of $1,500,000 will permanently name and support a faculty chair 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.

The Kellogg Graduate School of Science and Technology

In 1989, 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. In honor of their extraordinary contributions to science and education, TSRI has named its graduate college "The Kellogg School of Science and Technology" for philanthropists Janet R. ("Jean") Kellogg and W. Keith Kellogg II.

We believe that TSRI'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 | Gifts of all sizes are welcome. A gift of $24,500 will name and support a graduate stipend for one year. A commitment of $500,000 will endow a graduate student stipend in perpetuity. A commitment of $10,000,000 will endow the Graduate Program.

Educational Outreach Programs

As one of the country's leading basic biomedical research institutions, TSRI has made a commitment to the local science education community to use its intellectual and material resources to expose high school and undergraduate students and middle and high school science teachers to contemporary issues in biomedical research, to provide an intensive, hands-on laboratory experience, and to encourage students to pursue scholarship and careers in the biological and chemical sciences. TSRI's multi-faceted Educational Outreach Programs represent a cornerstone of the institute's commitment to training the next generation of scientists and perpetuating scientific knowledge.

At this time, the program capacity of TSRI's summer research internship program 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 in filling these slots is availability of funding.

Giving Opportunities | Gifts of all sizes are welcome. A contribution of $2,500 supports the participation of one high school or undergraduate student in the summer internship program. A contribution of $5,000 supports the participation of one middle or high school teacher in the summer internship program. A contribution of $1,000,000 can name and endow the entire program.

Endowments

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

Giving Opportunities | Gifts of all sizes are welcome. 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 and needs within our Educational Outreach Programs can be endowed with gifts of $100,000 and up.

Equipment Acquisition

TSRI enjoys one of the world's leading private computational capabilities with an array of computers. 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.

The Kresge Library

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 students and faculty since the 1970s and are in need of replacement.

Giving Opportunities | Gifts of all sizes are welcome.

Gifts to The Scripps Research Institute

Gifts to The Scripps Research Institute (TSRI) provide the assurance that the 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 carry-over 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, or 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, or 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 methods of giving, please contact:

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10550 N. Torrey Pines Rd.
Mail Drop TPC-2
La Jolla, CA 92037
(858) 784-9367
(800) 788-4931
(858) 784-2608 FAX

Benefits of Giving

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. 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 yearly report outlining the impact of your gift;
- An invitation to 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;
- 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,* which discusses developments at The Scripps Research Institute, the latest clinical procedures available to our patients, and overall advances made at TSRI and Scripps Health; and
- TSRI *Endeavor,* a publication of scientific progress, awards received, and publications made by TSRI scientists and TSRI *Endeavor* Year In Review, which recognizes supporters of TSRI.

Scripps Legacy

We also recognize lifetime cumulative giving at the following levels:

Associate
$25,000 - $99,999

Advocate
$100,000 - $249,999

Ambassador
$250,000 - $499,999

Sponsor
$500,000 - $999,999

Guarantor
$1,000,000 - $2,499,999

Patron
$2,500,000 - $4,999,999

Benefactor
$5,000,000 - $9,999,999

Founder
$10,000,000 or more

Additional benefits include:

- Your name listed on the Scripps Foundation's *Annual Report on Philanthropic Support.*

Those giving at the Advocate level or above also receive:

- Name recognition on the Honor Roll Boards in the lobbies of all Scripps Health Hospitals.

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 or our Legacy program, please contact:

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