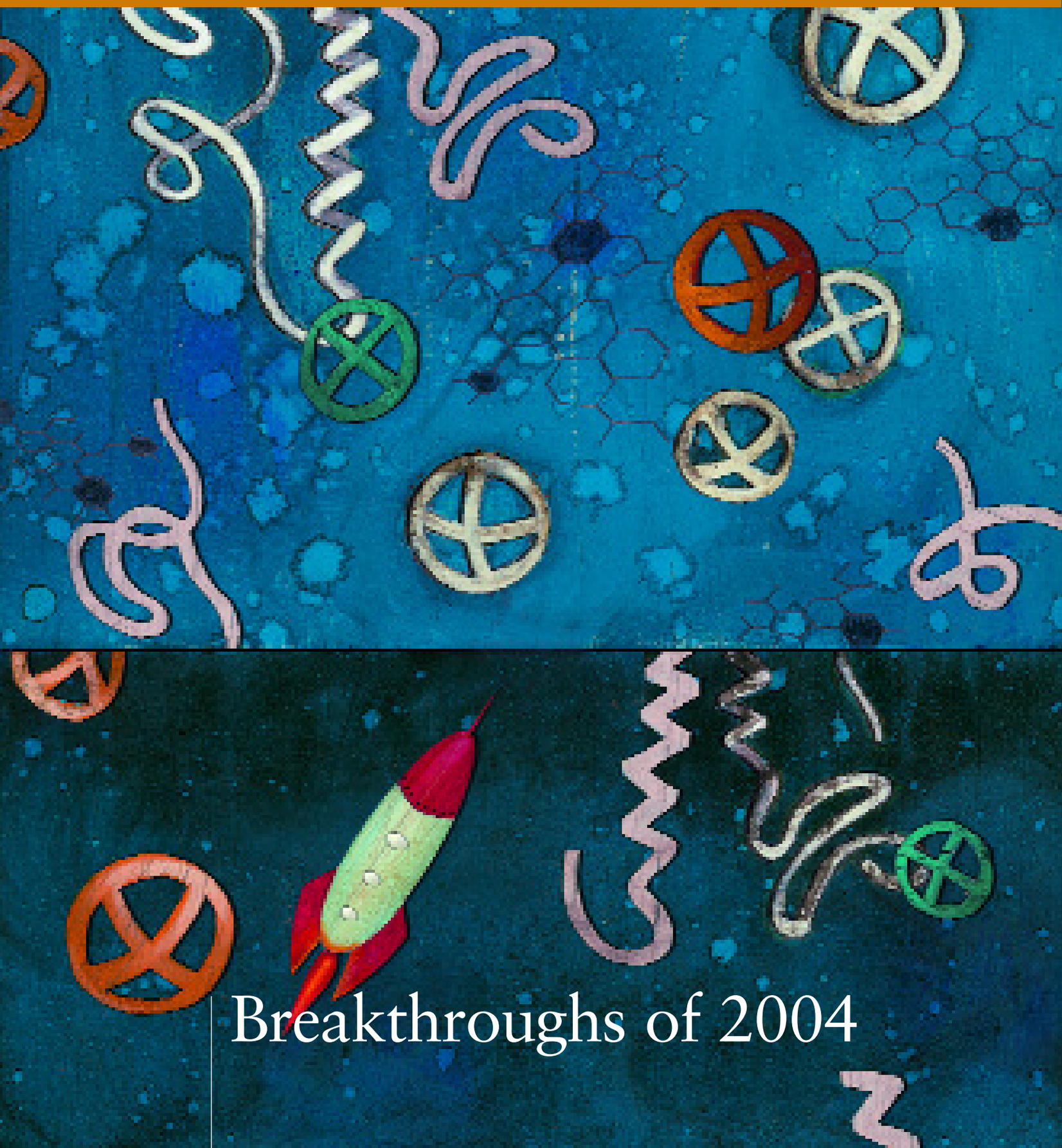
VOLUME SEVEN NUMBER THREE

Endeavor



Breakthroughs of 2004

Endeavor

VOLUME SEVEN | NUMBER THREE
Winter 2004/05

This issue of *Endeavor* magazine features breakthroughs of 2004 at The Scripps Research Institute. Among many significant scientific milestones this year: the development of potential treatments for certain kinds of blindness that currently have no cure, significant findings on the molecular roots of alcoholism, innovative therapeutic strategies for heart attack and stroke, and a new hypothesis on the causes of Alzheimer's and Parkinson's diseases.

featured

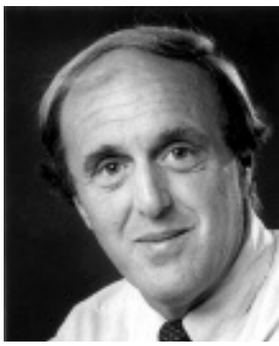
also

ENDEAVOR IS A PUBLICATION OF THE SCRIPPS RESEARCH INSTITUTE

Year in Review 2004

PRESIDENT'S INTRODUCTION

Leadership is about many things: a passionate commitment to pursuing your goals, a vision for the future and an adherence to staying the course, a record of solid performance and achievement, a spirit of innovation and creativity. As an organization, I believe that The Scripps Research Institute has firmly established its leadership position in the international scientific community by remaining true to these basic tenets, by continuing to promulgate a record of outstanding scientific achievements, by attracting extraordinarily talented scientific faculty, staff, students, and board members, and by extending the reach of its capabilities by developing our major new initiative in Florida. Simply stated, it has been an exceptional year for Scripps Research.



Richard A. Lerner, M.D., president of The Scripps Research Institute.

SCRIPPS FLORIDA MOVES FORWARD

Substantial progress has been made in shaping the scientific scope of the Scripps Florida enterprise and in recruiting a robust roster of scientific faculty and administrative management. Our first announcement early this year was the recruitment of internationally renowned scientist Charles W. Weissmann, M.D., Ph.D., a pioneer in modern biomedical research and molecular biology. Formerly senior research scientist in the Department of Neurodegenerative Diseases at the University College of London, he heads the Scripps Florida Department of Infectology. Among Professor Weissmann's research interests are the pathogens that cause malaria and tuberculosis, and such prion diseases as mad cow disease.

More recently, we have announced the recruitment of noted chemist William R. Roush, Ph.D., as professor of chemistry, executive director of medicinal chemistry, and associate dean of the Florida graduate programs. Currently the Warner Lambert/Parke Davis Professor of Chemistry and chair of the Department of Chemistry at the University of Michigan, he will begin work at Scripps Florida in early 2005. Dr. Roush is recognized for his groundbreaking research in the analysis, structural determination, and synthesis of complex, biologically active, natural products that may lead to the development of new drugs. Further, he has been a mentor to two generations of chemists, a role he will continue with Scripps Florida graduate students and postdoctoral fellows.

We have created the framework for the scientific research that will be undertaken at Scripps Florida, including developing leading edge technologies to enable scientists to examine the basic biology of human health and find new and better treatments for a variety of devastating human diseases. These programs have been specifically designed to answer the most important questions in biology and medicine and will address such diseases as AIDS, cancer, diabetes, obesity, prion disease, Parkinson's, and schizophrenia. The new research programs encompass scientific inquiry in the areas of genetic disease informatics, cancer biology, infectology, the genetics of complex diseases, proteomics, nuclear hormone receptors, drug metabolism and pharmacokinetics, diabetes and obesity, medicinal chemistry, cell-based screening,

and HIV therapeutics. Further, we have recruited more than 20 highly accomplished scientists who will carry out much of the research in these new programs. They have previously held positions and appointments at many of the finest academic institutes and private companies in the world, and we are very pleased that they have made the commitment to join us at the inception of our research efforts in Florida.

Executive management expertise is critical to the efficient operation of research activities. Toward this end, we have appointed Harry W. Orf, Ph.D., as vice president of scientific operations for Scripps Florida to oversee the administration and management of scientific services that will support biomedical research there. For the past 21 years, he has served as director of the Molecular Biology Laboratories at Massachusetts General Hospital in Boston; he also is a principal associate in genetics at Harvard Medical School. His management and administrative experience also includes memberships of the boards of directors of several biotechnology companies.

"As an organization, I believe that The Scripps Research Institute has firmly established its leadership position in the international scientific community..."
– Richard A. Lerner

We also appointed William E. Ray, Ph.D., to our team, first as director of external affairs for Scripps Florida, then as vice president of external affairs for all of Scripps Research. Dr. Ray comes to Scripps from the Palm Beach County Cultural Council, where he was president and CEO for more than 20 years.

NEW MEMBERS TO THE BOARD OF TRUSTEES

At no time in the history of the organization has strong leadership from the Board of Trustees been more important in making decisions that will leave an indelible mark on the future of Scripps Research. This year, we have been fortunate in recruiting five distinguished and accomplished individuals to our board. Alexander W. Dreyfoos owns and directs The Dreyfoos Group, a private capital management firm that grew out of his previous ventures, including Photo Electronics Corporation and WPEC-TV12, the CBS network affiliate in West Palm Beach. Andrew J. Viterbi, Ph.D., is head of the Viterbi Group, LLC, a firm he co-founded to advise and invest in start-up companies. He also is the co-founder of QUALCOMM, a leading developer and manufacturer of mobile satellite communications and digital wireless telephony, and professor emeritus at the University of California San Diego.

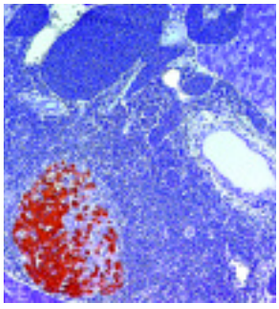
Scripps Florida has begun to recruit a robust roster of scientific faculty and administrative management, including (clockwise) investigators Charles Weissmann, M.D., Ph.D., William Roush, Ph.D., Teresa Reyes, Ph.D., and Patrick Griffin, Ph.D.

Phillip Frost, M.D., is a clinical professor of dermatology at the University of Miami School of Medicine. He also has served in leadership positions with many corporations and organizations, and is presently a director of Northrop Grumman Corporation, a governor of the American Stock Exchange, chairman of the board and CEO of IVAX Corporation, and chairman of the Board of Trustees at the University of Miami. J. Michael Cook, retired chairman and CEO of Deloitte & Touche LLP, is also chair of the Deloitte & Touche Foundation and a member of the board of Deloitte & Touche Tohmatsu. Mr. Cook has been a leader in his profession, serving as immediate past chairman and president of the Board of Trustees of the Financial Accounting Foundation, and is active as a member of the board of such companies as The Dow Chemical Company, Northrop Grumman

Corporation and the Fidelity Group Mutual Funds. Lawrence F. De George, V.M.D. is chairman and CEO of LPL Investment, Inc., and LPL Group, Inc., in West Palm Beach. He also is founder and chairman of CompleTel LLC, a competitive local exchange carrier in Amsterdam and Paris; director of United Global Communications, Inc.; founder and chairman of Cervalis; and founder and director of Advanced Display Technologies.

SIGNIFICANT RESEARCH DISCOVERIES

The laboratory of Peter Schultz, Ph.D., continues its prolific efforts on a variety of research fronts. He has directed a group of scientists at Scripps Research and the Genomics Institute of the Novartis Research Foundation in identifying a small synthetic molecule that can control the fate of embryonic stem cells. The compound, cardiogenol C, causes mouse embryonic stem cells to selectively differentiate into "cardiomyocytes," or heart muscle cells, an important step on the road to developing new therapies for repairing damaged heart tissue. Stem cells have huge potential in medicine because they have the ability to differentiate into many different cell types—potentially providing cells that have been permanently lost by a patient. Schultz et al. continue their work toward an understanding of the exact biochemical mechanism whereby cardiogenol C causes the cells to differentiate into cardiomyocytes, as well as attempting to increase the efficiency of the process.



A group of scientists has found a connection between poor T cell survival and the development of autoimmune disease.

In another study, a Schultz research team has demonstrated the simultaneous incorporation of two unnatural amino acids into the same *Escherichia coli* polypeptide, demonstrating that the genetic code is amenable to expansion to 22 amino acids. For years, scientists have created proteins with such unnatural amino acids, but until Schultz and his colleagues began their work several years ago no one had ever found a way to get unnatural amino acids into the genetic code. This latest result opens the door for making proteins within the context of living cells with three, four, or more additional amino acids at once. The discovery has implications in medicine, as many proteins used therapeutically need to be modified with chemical groups such as polymers, crosslinking agents, and cytotoxic molecules.

"[This year] the collective contributions of those involved in the Scripps Research enterprise elevated the organization to a new level." – Richard A. Lerner

Dr. Schultz and Chi Huey Wong, Ph.D., professor in the Department of Chemistry and The Skaggs Institute for Chemical Biology, have developed a new way of making glycoproteins—proteins with carbohydrates attached. Methods for making these proteins are not only important to scientists who want to understand the role of carbohydrates in protein structure and function, but also to physicians since pharmaceuticals are often heavily glycosylated proteins. This strategy, which avoids some of the bottlenecks of previous methods, is scalable and should be less expensive than other current methodologies.

Kim Janda, Ph.D., who holds the Ely R. Callaway Chair in Chemistry and is an investigator in The Skaggs Institute for Chemical Biology, has designed a potentially valuable tool for treating cocaine addiction by creating a modified "phage" virus that soaks up the drug inside the brain. His research group coated the virus with an antibody that binds to molecules of cocaine and helps to clear the drug from the brain, which could suppress the positive

Scripps Research scientists have elucidated the structure of a protein from the deadly 1918 "Spanish flu" virus—a virus that took more lives than World War I.

reinforcing aspects of the drug by eliminating the cocaine "high." Phage particles, like many types of viruses, have the ability to enter the brain through the internasal passageway. The scientists used this ability to deliver their antibody into the central nervous system, thereby reducing one effect of cocaine in rodent models. While this technique could be useful as a general strategy of delivering therapeutics into the brain, the approach has not yet been tested clinically in humans.

A group of scientists led by Nora Sarvetnick, Ph.D., professor in the Department of Immunology, has found a connection between poor T cell survival and the development of autoimmunity. Because of this linkage, they have proposed a new hypothesis about the cause of autoimmunity, asserting the need for a certain level of immune stimulation to fill the body with immune cells. An understimulated immune system results in too few T cells, and the body tries to correct the condition by inducing a vigorous expansion of the remaining T cells, creating a more autoreactive population. This provides a new way for thinking about how to make autoimmune diseases more preventable. The scientists postulate that the key to decreasing the chances of developing autoimmunity may be to stimulate the immune system by priming people with germs.

Ian Wilson, Ph.D., molecular biology professor and a member of The Skaggs Institute for Chemical Biology, and his colleagues have elucidated the structure of a protein from the deadly 1918 "Spanish flu" virus—a virus that took more lives than World War I and became the largest and deadliest influenza outbreak in recorded history. Seeking to discover why the outbreak was so devastating, the team described the structure of a protein called hemagglutinin, the first structure of this extinct virus to be solved. This structure has features found primarily in avian viruses and reveals details that may be crucial to understanding the outbreak. Avian-to-human transmission is rare, and because of this, has the potential to be more deadly. Because the surface proteins of the virus were different from those found on other flu viruses, people's immune systems were unaccustomed to them and unable to fight off the Spanish flu.

A team of researchers led by Martin Friedlander, M.D., Ph.D., has been able to preserve visual function in mice that were genetically predisposed to developing retinitis pigmentosa, a profound degenerative eye disease. After injecting adult bone marrow-derived stem cells from mice or humans into the back of mouse eyes at an appropriate stage of development, they had a completely normal retinal vasculature and significantly improved retinal tissue. They also responded to light. This approach could potentially be used to treat disorders of the retina that involve vascular and neuronal degeneration. More than 100,000 Americans suffer from retinitis pigmentosa, which is caused by more than 100 different genetic mutations. Currently, there is no way to treat or even slow the course of the disease.

GRANT ESTABLISHES PEARSON CENTER FOR ALCOHOLISM AND ADDICTION RESEARCH

In early 2004, Scripps Research received a gift of $3 million to establish The Pearson Center for Alcoholism and Addiction Research, which combines biomedical research with clinical applications to fight these deadly and costly diseases. In co-directing the center, Professor George F. Koob, Ph.D., who heads the Division of Psychopharmacology in the Department of Neuropharmacology, collaborates with Professor Barbara Mason, Ph.D., who heads its Division of

Clinical Pharmacology. Of particular interest to the scientists are the physiological changes in the brain that drive excessive drinking and create vulnerability to relapse. They study the viability of utilizing new compounds, designed at Scripps Research and elsewhere, to modulate the neurological effects of alcohol and reduce excessive intake and/or relapse. Scripps Research received the grant from an anonymous donor on behalf of family and friends who have suffered from the devastating consequences of the disease.

FAREWELLS

Few people are worthy of being known as a gentleman and a scholar, but this was an entirely apt description of our colleague, friend, and Scripps Research medical scientist, Bernard M. Babior, M.D., Ph.D., who died this year after a long battle with prostate cancer. For the past 18 years he was a professor and head of the Division of Biochemistry in the Department of Molecular and Experimental Medicine at Scripps Research and a staff physician at Scripps Clinic. Dr. Babior was noted for his groundbreaking insights into human biochemistry, particularly as they pertained to the body's defenses against infection. He contributed so much during his long tenure, not only by invaluable research that has enriched the scientific community, but also through his humanity and his sense of serving those with whom he interacted. We miss him dearly.

In a lasting tribute to a former colleague and one of the original scientists at Scripps, William O. Weigle, Ph.D., a sculpture entitled "Oak Cairn" by renowned British artist Andy Goldsworthy, was installed on the La Jolla campus. Dr. Weigle, who died in 2001, was one of the immunologists who came from Pittsburgh in 1961 to establish the Division of Experimental Pathology at Scripps Clinic and Research Foundation. The work of this group attracted others and the research program flourished and diversified, forming the basis of the modern-day Scripps Research. Dr. Weigle leaves a permanent legacy of seminal contributions to the field of immunology, and contributions to the lives of those he trained and colleagues with whom he worked for 40 years at Scripps and throughout the world.

A sculpture entitled "Oak Cairn" by renowned British artist Andy Goldsworthy, pays tribute to one of Scripps Research's founding scientists, William O. Weigle, Ph.D.

"I am proud and honored to work side by side with our colleagues in La Jolla and in Florida, as we create a new vision for the future of Scripps Research, and position the Institute to assume an even greater role in the scientific community in the years ahead." – Richard A. Lerner

This represents another year of extraordinary effort on the part of our scientists, board members, donors and friends of the institute, students, and technical and administrative support staff. It was a year in which the collective contributions of those involved in the Scripps Research enterprise elevated the organization to a new level. I am proud and honored to work side by side with our colleagues in La Jolla and in Florida, as we create a new vision for the future of Scripps Research and position the institute to assume an even greater role in the scientific community in the years ahead.

Richard A. Lerner, M.D.

Martin Friedlander, M.D., Ph.D., poses in front of a sculpture representing the retina which contains rod and cone cells—a focus of his studies.

Research Offers New Hope in the Search to Treat Blindness

MARTIN FRIEDLANDER EXPLORES THE POTENTIAL OF STEM CELL THERAPY FOR RESTORING VISION

Plato believed that the human eye sent emissions to an object enabling it to be seen. Aristotle believed people could see because of a process in the space or "medium" between an object and the viewer's eye.

Science has since explained a considerable amount of the underlying biochemistry of vision and has even made progress in describing the process of the interplay between objects, light, and the eye itself. But science is still grappling with an understanding of the loss of vision and how to remedy it. Now, the development of a unique therapeutic technique offers new hope in the search for a way to treat some kinds of blindness.

Associate Professor Martin Friedlander, M.D., Ph.D., and researchers in the Department of Cell Biology at The Scripps Research Institute and the Jules Stein Eye Institute at the University of California Los Angeles David Geffen School of Medicine have discovered a potential approach for treating retinal degenerative diseases. Inherited retinal degenerative diseases afflict one in every 3,500 people in the United States.

Retinitis pigmentosa, for example, often appears in adolescence and can lead to total blindness by adulthood. According to the National Eye Institute, more than 100,000 Americans suffer from retinitis pigmentosa. Currently, there is no way to treat patients with this condition and no way to slow the disease.

In research supported by the National Eye Institute, the Kovner family, and Eli Callaway, Friedlander and colleagues administered adult bone marrow stem cells into the eyes of mice genetically predisposed to develop retinal degeneration. This therapy stabilized blood vessels in the eye and prevented the degeneration of a specific type of photoreceptor (cones) used in humans for fine and color vision, restoring some vision to the mice. These breakthrough findings could eventually lead to new therapies to help people see.

"If someone told me 15 years ago that you could take human bone marrow stem cells and use them to treat blindness, I wouldn't have believed it," Friedlander says.

STEM CELLS: A WORLD OF POSSIBILITIES

Stem cells are the building blocks of living organisms. In humans, they develop into the various cells that form our bodies. While most cells in the body have specific functions (such as heart muscle and skin cells), stem cells remain "neutral" and pluripotent—capable of forming various types of cells—until they receive special signals to develop into specialized cells. Renewable and plentiful, they can serve as a source of cells to replenish our damaged and diseased tissue as we get older.

Stem cells were first discovered in adult tissues 30 years ago. They exist in bone marrow, blood, skin, skeletal muscle, dental pulp, the cornea and retina of the eye, the lining of the gastrointestinal tract, the brain, liver, and pancreas. For a long time, adult stem cells were believed to develop only into cells of the particular tissue from which they were derived. But some adult stem cells are now known to be more versatile.

"If someone told me 15 years ago that you could take human bone marrow stem cells and use them to treat blindness, I wouldn't have believed it."
–Martin Friedlander, M.D., Ph.D.

The recent controversy over stem cell research primarily involves stem cells derived from human embryos, a process that destroys the embryo. In contrast, adult stem cells can be obtained with little harm to the donor. Also, because adult stem cells can be taken from the patient's own body, they are less likely to be rejected by the patient's immune system. What fascinates Friedlander about adult stem cells, he says, "is the possibility that we're all walking around with cells that we could use therapeutically to treat potentially devastating diseases."

Adult stem cells have already shown promise in human patients to improve heart functions, to restore healthy blood cell formation, and to treat multiple sclerosis, Crohn's disease, and Parkinson's disease. →

LAYING THE FOUNDATIONS

Friedlander's professional interest, though, lies in disorders of the eye. As a specialized discipline, ophthalmology has given Friedlander entry into two worlds.

"When you're doing both medicine and science you try to find a way to combine both careers," he says. "If you choose the right specialty, recognize your limitations, and keep your focus, it is possible to provide patients with first-rate care and still maintain an edge in the laboratory."

In this case, work in the laboratory enabled Friedlander and his colleagues to build on previous discoveries in their quest to look for new and better ways of treating eye disease. In a study published in *Nature Medicine* in 2002 Friedlander and his team found that adult bone marrow stem cells could target to sites of new blood vessel formation and, by becoming incorporated into the forming vessels, help stabilize and control a vasculature that would ordinarily degenerate.

Using the kind of bone marrow stem cells that can form blood vessels, Friedlander and his colleagues treated mice genetically predisposed to develop retinal degenerative disease. Normally, these mice will begin to lose retinal blood vessels two weeks after birth and within a month become completely blind. But the study showed that when stem cells are injected into the eye, they become incorporated into developing blood vessels to form "mosaics" with the existing blood vessel cells.

"It's a rare privilege to see things spill over so directly from bench to bedside and this is one case where we might see direct benefit for our patients in the future."
–Martin Friedlander, M.D., Ph.D.

"The new cells contribute to a certain level of strength in the blood vessel, making it resistant to degeneration," Friedlander explains.

These early studies, says Friedlander, reveal the potential of stem cells for actually restoring vision. "This first set of experiments showed us that we could target adult bone marrow-derived stem cells to form retinal blood vessels and that these mosaic vessels would be highly stable, even in the face of disease that ordinarily makes the vessels degenerate. After this treatment, not only were the vessels more stable, but also the neural retina was present in mice with a disease that ordinarily completely destroys the photoreceptors. The real question was whether the mice actually retained vision along with the photoreceptors. We decided to pursue this direction of research."

The results, he adds, were "a pleasant surprise."

In new work published in the *Journal of Clinical Investigation* in September, Friedlander and his team report that the stem cell therapy can fully rescue retinal blood vessels preventing further retinal degeneration when injected into mice up to two weeks after birth. More significantly, the rescue appears to restore vision by "saving" photoreceptor cone cells in the retina.

The retina is the light-sensing area of the eye. It contains rod cells, which help us see in low light, and cone cells, which enable us to see color and detail. Much like film on the back of a camera which needs a chemical emulsion coating and light to create photographic images, the retina needs to have a rich blood supply to function. Blood is supplied to the area from vessel layers under, on top of, and within the retina. In certain degenerative diseases, the top layer of blood vessels remains, but the two deep layers degenerate along with the photoreceptors that have the underlying genetic defect.

But by targeting the retina with appropriate stem cells, Friedlander's team found that "whenever we rescued the vessels, we also rescued the outer nuclear layer—the section containing the photoreceptors—of the retina."

The research provides new information about the relationship between the rescue of blood vessels and the functions those blood vessels support. "Originally we thought that once the retina goes, you don't need the vessels anymore," he says. "But it's not simply a matter of the vessels existing to nourish the retina. There's some sort of cross-talk between the retina and blood vessels that ensures vision."

DISCOVERING THE DETAILS

Once Friedlander and his team discovered the rescued retinas, they looked at whether or not the treated mice could actually see.

"A mouse can't read for us, so we do electroretinograms using light to record electrically whether the mouse sees light," Friedlander explains.

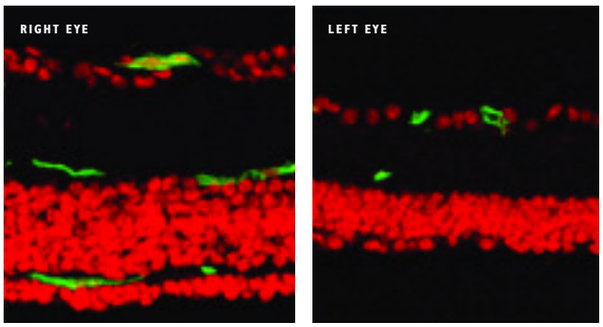
In the control eye, which had not been treated, the researchers found no measure of sight. But the treated or rescued eye revealed electrical stimulations. Although the electroretinogram wasn't normal, the activity suggests the mouse can see something with that eye.

The rescue effect lasted for up to six months after treatment and was found to be most effective when the stem cell therapy is administered before complete retinal degeneration occurs, Friedlander says.

Friedlander's team then looked at which cells were being rescued. "The rescued retinas were remarkable;

what was left were all cones," Friedlander says. "We are selectively rescuing cones, making them resistant to whatever kills them when rods degenerate."

This discovery is significant because the majority of inherited human retinal degenerations affects rods (which help the eye see in dim light), while the death of cones (which help the eye see color and detail) is secondary. "So, in theory, if you could rescue cones, you could retain healthy central vision," Friedlander says.



The Friedlander lab has found a way to rescue retinal function in models predisposed to developing retinal degenerative disease. Contrast the right eye, treated with stem cells derived from adult bone marrow, with the left, untreated. *(Journal of Clinical Investigation by Martin Friedlander. Copyright 2004 Am. Soc. for Clinical Investigation. Reproduced with permission of Am. Soc. for Clinical Investigation in the form at Magazine via Copyright Clearance Center.)*

While Friedlander's team does not know yet exactly how the rescue effect works, they have been able to identify a class of proteins called "heat shock" proteins in the rescued retinas and rescued cone cells. "These proteins are expressed in response to stress and serve to make a cell resistant to certain types of stress-related death," Friedlander says. In other words, the cone cells can protect themselves once the rod cells die.

"We're not curing the underlying gene defect. The rods still die. But the cones seem to be more stable," he notes.

This finding points to the possibility of preventing further vision loss in mice and eventually in human eyes. "By making the cones resistant to this 'innocent bystander' death secondary to loss of the rods, in theory, we should be able to maintain central vision in these patients," Friedlander says.

TREATING DISEASE WITH HEALTHY CELLS

In the treatment, Friedlander and his team acquired the same results when using bone marrow stem cells from humans or from mice both with and without retinal degenerative diseases. This holds positive implications for future stem cell treatment of this kind on humans, as patients with vision loss could supply their own bone marrow stem cells.

"You don't have to worry about rejection in the recipient. That's a real advantage," Friedlander says.

The new stem cell therapy offers possibilities for a simple treatment for vision loss in humans. Because more than 100 mutations in different genes cause retinal degeneration, treating each of those genes would be extremely difficult. "The beauty of this is that it's a generic treatment," Friedlander points out. "It's like treating atherosclerosis not by ripping out the plaques (fatty deposits in the arteries that can constrict the flow of blood to vital organs), but by preventing the plaques from developing to begin with."

Further research will reveal how the treatment might actually work on humans suffering from vision loss. Friedlander recognizes that before stem cell therapy can be used in clinics, more questions must be answered. "Are stem cells safe? Do they have side effects? What about dosing? With more than one injection can we get a better effect?"

One of the study's authors, John Heckenlively, M.D., now at the University of Michigan Kellogg Eye Center, says the research offers an innovative approach for the possible treatment of vision loss. "This particular approach is encouraging because you get rescue of cells and can halt some of the retinal degeneration. Nothing else has been shown to do that at this stage."

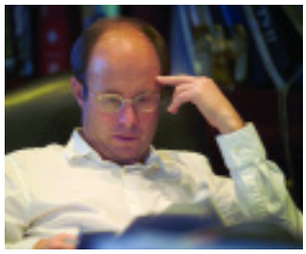
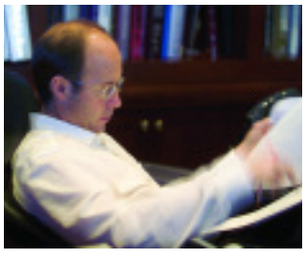
Heckenlively adds that further research is needed to explore the therapy with different types of retinal degenerative diseases and to explore more fully the optimal use of the stem cells. "This is just preliminary data, but the first step is to show that we can intervene in the degeneration," Heckenlively says. Friedlander, a medical doctor who has worked with patients with retinal degenerative conditions for nearly 15 years, says he is hopeful about the possible links between what he's learning in the laboratory and what he might someday use in the clinic. "It's a rare privilege to see things spill over so directly from bench to bedside and this is one case where we might see direct benefit for our patients in the future."

Currently, Friedlander spends one day a week with patients. He says he looks forward to the possibility of clinical trials with stem cell therapy. "For a lot of these diseases we don't have treatments or cures, so providing my patients access to safe clinical trials that may prevent or reverse deterioration of their vision is great. My patients would give almost anything to save their vision and with recent advances in our knowledge of the science underlying sight it may now be possible to offer them hope in the form of potential treatments."

•Kimi Eisele

Working to Solve the Alzheimer's and Parkinson's Puzzles

JEFFERY KELLY PROPOSES A NEW EXPLANATION FOR NEUROLOGICAL DISORDERS


Scripps Research investigator Jeffery Kelly, Ph.D., focuses on the role of inflammation in Alzheimer's and Parkinson's diseases.

Some faculty and staff at The Scripps Research Institute are already in on the secret: there are two Jeffery Kellys. The more familiar one serves as dean and vice president of academic affairs, and Lita Annenberg Hazen Professor of Chemistry. The other Jeffery Kelly loves to get behind the wheel of his 1974 Porsche 911RS and roar competitively around a curvy track, averaging speeds of nearly 90 MPH.

Clearly, he's a man in love with motion.

But he's more interested in talking about the movement—sometimes quick, sometimes exasperatingly slow—of scientific discovery. His most recent work, conducted in collaboration with the Lerner laboratory, offers a novel approach to untangling the mysteries of amyloid disorders common to Alzheimer's and Parkinson's diseases, and could lead to a much clearer understanding of both.

Many people reading these words have lost a grandfather, a grandmother, a father, a mother, a sibling, or friend to the all-demanding claims of Alzheimer's. As baby boomers have aged, the number of people in this country with Alzheimer's disease and related disorders has grown. Newly published research suggests that 4.5 million Americans now have Alzheimer's and that the numbers will swell to as many as 16 million by mid-century unless a cure is found.

Here are a couple of other facts about Alzheimer's. The disease now strikes more than one in 30 Americans, slowly causing memory loss, confusion, and, ultimately, death. Incidence increases with age—about half the population that lives past 85 gets Alzheimer's. And the disease is the third most costly in the United States, each year draining $100 billion from the U.S. economy.

Parkinson's is another chronic neurological disease. It affects a small area of nerve cells in a part of the brain known as the substantia nigra that normally produces a chemical—dopamine—that helps direct muscle activity. Those with Parkinson's experience trembling in the arms, legs, jaw, and face, stiffness in the limbs and trunk, slowness of movement, and impaired balance and coordination. A subset of this population also experiences other symptoms, including dementia. The disease gets progressively worse over time, often coming to interfere with walking, talking, and other everyday activities.

Approximately one million Americans have Parkinson's disease, including three out of every 100 people over age 60. More than 50,000 Americans are diagnosed with the disease each year and the disease drains $5.6 billion from the American economy annually.

Kelly's recent work is focused on inflammation and its role in the etiology of Alzheimer's and Parkinson's diseases.

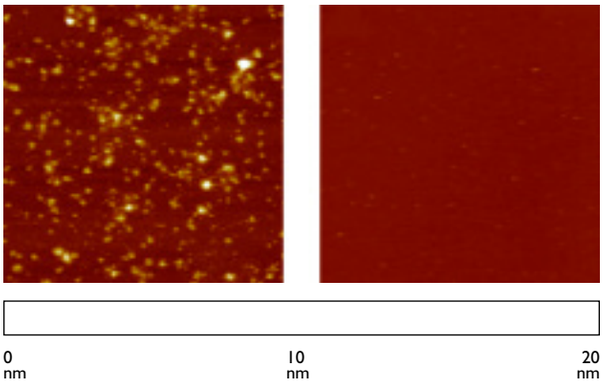
> *"It's well known that high cholesterol is a risk factor for both heart disease and neurodegenerative diseases, so I started thinking about whether the explanation, in terms of a risk factor, might not be metabolite modification of proteins. I wondered if the same risk factors could play a role in Alzheimer's and Parkinson's diseases."* –Jeffery Kelly, Ph.D.

INFLAMMATION AND YOU

The idea of inflammation may be locked in the public mind by TV commercials: perhaps a close-up of a woman's elbow radiating heat, flames even, as she groans in pain with arthritis. And Kelly says this image is at least a starting point for the non-scientist to understand the physiology of inflammation. →

"What occurs within a flame is an oxidative process, and when your immune system attacks a foreign invader, your system rallies its oxidation-mediating small molecules to damage the invader to the point where it's no longer viable," says Kelly. "It's the normal response to tissue injury for bacterial or viral infection. We absolutely need the inflammatory response to fight these infections."

So inflammation in moderation is a good thing. It becomes a problem when the response is chronic—when the immune system is stimulated by some abnormal process, such as protein aggregation, which can lead to the oxidation of useful molecules in the body referred to as metabolites, converting them into abnormally reactive metabolites.



The Kelly lab shows that a certain metabolite modifies proteins causing them to misfold (left), unlike a control (right). *(Copyright 2004 National Academy of Sciences, USA.)*

But we're getting ahead of the story. In deciding to follow the inflammation trail to see where it might lead, Kelly looked to breakthroughs by one of his Scripps Research colleagues. In fact, Kelly credits a recent research project headed up by Scripps Research President Richard Lerner, M.D., as "absolutely the spark that got me thinking about the role of inflammation in Alzheimer's." Last November a team of investigators led by Lerner and Scripps Research Associate Professor Paul Wentworth, Jr., Ph.D., reported new findings that ozone is produced in fatty atherosclerotic plaques taken from diseased arteries. Ozone is a highly reactive molecule that has never before been considered part of biology.

In their report, Lerner, Wentworth, and their colleagues describe how ozone can trigger pathological changes in other molecules in the body, like cholesterol, which ozone breaks down to produce toxic compounds. The scientists describe two such compounds, which they call the "atheronals." These atheronals were found in atherosclerotic plaques that were surgically removed from patients with atherosclerosis.

"It was the atherosclerosis connection that got me going," Kelly says. "It's well known that high cholesterol is a risk factor for both heart disease and neurodegenerative diseases, so I started thinking about whether the explanation, in terms of a risk factor, might not be metabolite modification of proteins such as the ones whose aggregation is central to the pathology of neurodegenerative diseases. I wondered if the same risk factors could play a role in Alzheimer's and Parkinson's diseases."

A NEW HYPOTHESIS

Kelly's hypothesis is that some initial precipitating event, such as infection or head trauma, triggers inflammation, which, in turn, creates abnormal metabolites from normal brain molecules. These metabolites then modify the beta amyloid protein in the brain, according to the theory, causing the peptides to misfold into amyloid. Misfolded beta amyloid proteins are thought to be a major cause of Alzheimer's and some other neurological diseases because they can accumulate into fibrils and plaques in the brain.

To begin to test this hypothesis, Kelly, Lerner, and their colleagues have so far examined the postmortem brains of Alzheimer's patients and Parkinson's patients, and have compared each group to age-matched controls. Working with Kelly in his lab is "a whole cadre of people"—about 20 grad students, postdocs, and visiting scientists.

They found evidence of atheronals in the brains of the Alzheimer's patients, Parkinson's patients, and in age-matched subjects.

The levels of atheronals in the brains of the Alzheimer's patients were not significantly elevated compared to the control subjects, but this is not necessarily surprising, says Kelly. "According to this hypothesis, the propagation of misfolding and the buildup of fibrils inside the brain does not depend upon continuous exposure to abnormal and reactive metabolites, but to a precipitating event that may have occurred a decade or more earlier. What's extremely tricky about investigating this process is that these events take place over a number of years. A lot of these changes may be occurring over a decade or more, which makes the stages very difficult to delineate."

Though the levels of atheronals in the brains of the Alzheimer's patients were not significantly elevated, that wasn't the case with the brains of people stricken with what's called sporadic Parkinson's disease. (Although some cases of Parkinson's can be clearly traced to genetic factors or chemical exposure, for the most part

the cause of Parkinson's is unknown. If there is no clear cause, the diagnosis is "sporadic Parkinson's disease.")

Because there is plentiful evidence of early oxidative stress in Parkinson's, Kelly thought that, if his hypothesis was correct, the team would find these metabolites in Parkinson's brains at higher levels than in age-matched controls. "And that's exactly what we did find. Parkinson's is caused by the misfolding of alpha synuclein, similar to the misfolding of the beta amyloid protein in Alzheimer's. The idea that oxidative stress plays a primary role in pathology is much more widely accepted at this point in time for Parkinson's than for Alzheimer's."

In addition to making findings on Alzheimer's and Parkinson's brains, researchers in the Kelly lab have been able to discover the mechanism by which the abnormal metabolites initiate the process of amyloid beta amyloidogenesis. "This mechanism is quite interesting in that the metabolites accelerate the early steps of the process, but I'll refrain from telling you the details, since we're about ready to publish on that," Kelly says. The lab's work is being supported with grants from the National Institutes of Health, the Skaggs Institute for Research, and the Lita Annenberg Hazen Foundation.

CAUSE AND EFFECT

While the researchers are working hard to provide supportive evidence for the inflammatory metabolite theory of Alzheimer's, this will be a difficult task, Kelly admits, because the presence of these abnormal metabolites is hard to detect years after they initiate the aggregation.

The crux of the difficulty in proving the hypothesis is that it's often hard to prove cause and effect. "The only way you can be very confident about causality is to design agents that inhibit some critical step in this process and show in a clinical trial that it's ameliorating the pathology," Kelly says, "and that's a tall order."

He adds, matter-of-factly, that like most new ideas, there's a subset of people who like it and a subset who aren't convinced. "It's our job to show beyond reasonable doubt that this hypothesis is likely true."

Scientific disagreement doesn't seem to bother Kelly. In fact, he thinks it's good for science.

"There has been a big argument in the Alzheimer's field for some time as to whether inflammation is an early event or whether it's a late event. Some people would argue that inflammation occurs in Alzheimer's disease when everything is over. There's another camp of people who have published a lot in the last three years showing that the neuro-inflammatory response of the brain is quite an early event, particularly in animals."

Are these two camps antagonistic? "Oh, we're friendly enemies," Kelly laughs. "But, you know, at the end of the day, the data wins—not the opinion-holders. And we all want the same thing: to understand what's going on in these horrible neurological diseases and how to prevent it."

"ALL ABOUT PEOPLE"

Asked what he might have done had he not become a scientist, Kelly hesitates, perhaps having some trouble imagining a life outside of science. He says, finally, that he probably would have become an entrepreneur, and that he's always been interested in how technology leads to new products.

So it's not too surprising that, based on work he's done at Scripps Research, Kelly has founded a biotechnology company, called FoldRx Pharmaceuticals. The company, based in Cambridge, Massachusetts, with a half-dozen employees, is working to discover and develop drugs for the treatment of neurodegenerative and peripheral amyloid diseases based on the creation of drugs that halt the misfolding of proteins and their resulting malfunction. FoldRx was formed in 2003 based on technology licensed from the Whitehead Institute at the Massachusetts Institute of Technology and from Scripps Research.

"We all want the same thing: to understand what's going on in these horrible neurological diseases and how to prevent it." –Jeffery Kelly, Ph.D.

Kelly came to Scripps Research in 1997 from Texas A&M University not because he was unhappy there, but because he couldn't pass up the opportunity to work with such distinguished colleagues, he says. "There was no push, all pull. The Scripps Chemistry Department was—and is—one of the top in the country, and along with the wonderful collegiality, I knew Scripps attracted exceptional graduate students. These were the two reasons I came here—it was all about people."

"Jeff has been a wonderful collaborator and is clearly one of the world's authorities in understanding how abnormal protein misfolding leads to disease," says Lerner. "He's also been an enormously effective dean and vice president of academic affairs here. When he came here, he was already a leader in his field, and his contributions since that time have continued to be impressive and significant."

•Jeff Worley

Value Added

DAVID CHERESH CONDUCTS BASIC RESEARCH WITH THERAPEUTIC POTENTIAL

They are the diseases of the industrialized world—heart attack, cancer, and stroke. In the United States, Western Europe, and Japan, heart attacks kill more people than any other disease; some published estimates have put the figure at more than two million a year. The common thread linking all three—aside from a variety of underlying risk factors—is vascular permeability and the growth or proliferation of new blood vessels, intertwined functions that play a significant role in determining the outcome for a patient affected by one of these conditions.

In a heart attack or stroke, for example, the sudden drop in tissue oxygen due to a blocked blood vessel—a condition known as hypoxia—activates a chemical cascade described by Professor David Cheresh, Ph.D., and his colleagues in The Scripps Research Institute's Department of Immunology. This cascade disrupts the adhesion of endothelial cells, which make up the lining of blood vessels, opening gaps in the endothelial cell matrix. The resulting vascular leakage increases the fluid (water) content of the affected tissue and thus cellular damage and tissue injury.

In research with significant implications for therapy, Cheresh found that disrupting this cascade stabilizes endothelial barrier function and prevents vascular leakage. As a consequence, heart and brain tissue are preserved, and the severity and long-term consequences of the attack are reduced.

If such a treatment were readily available to emergency medical teams, the chances are more patients would survive with less damage to their hearts and brains.

"What we do in our lab," Cheresh says, "is to make fundamental discoveries with the added hope that those discoveries will one day be developed toward an approach that helps patients with particular diseases. In essence, we pass the scientific baton to a commercial group that has the infrastructure and know how to develop new therapies—moving it from bench to bedside."

A SCIENTIFIC HOME

Scripps Research has been Cheresh's scientific home since he first arrived to do postdoctoral work with Professor Ralph Reisfeld, Ph.D., in 1982. Prior to that, Cheresh did his undergraduate work at the University of Michigan, then obtained his doctorate in microbiology and immunology from the University of Miami. Amazingly, he still works in the same laboratory he entered in 1982, occupying it for nearly a quarter century, a Scripps Research record. The name on the laboratory door, however, is now his.

"I've spent my entire career at Scripps," he says. "Right now, we have a great team of scientists because we've made a point of recruiting from all walks of life—bioengineers, immunochemists, biochemists, cell biologists, and physician scientists. [Scripps Research] is among the best places to do basic science because the science is never compromised. That allows us to approach a problem from any number of directions."

Initially, Cheresh and his laboratory colleagues were interested in the phenomenon of cell adhesion and the role specific adhesion and growth factor receptors played in the formation of new blood vessels, a process called angiogenesis, in cancer. (Two new therapeutic compounds were developed as a result of that work for the treatment of cancer, rheumatoid arthritis, and psoriasis; both are completing Phase II clinical trials with some good clinical responses in patients with inflammatory and malignant disorders.)

"What we do in our lab is to make fundamental discoveries with the added hope that those discoveries will one day be developed toward an approach that helps patients with particular diseases." –David Cheresh, Ph.D.

Because of that earlier work, Cheresh became interested in how this particular signaling pathway played out in endothelial cells, and how various growth factors and cell adhesion receptors stimulate blood vessel growth. When he discovered that certain kinases contributed significantly to endothelial cell function, Cheresh took a closer look at the blood vessel component of the process, and with it the problem of vascular leakage. →

A POTENTIALLY HELPFUL PROCESS TURNS DEADLY

Vascular leakage is a unique function associated with the growth factor VEGF, the only angiogenic growth factor that induces blood vessel permeability—leakage. Although the process seems almost perverse, Cheresh points out that leakage actually helps in certain disease states, especially cancer, where the body attempts to block tumor growth by surrounding it with fibrin, an insoluble protein needed for blood coagulation. Vascular leakage helps supply the necessary materials for new blood vessel growth in this fibrin barrier.

"[Scripps Research] is among the best places to do basic science because the science is never compromised. That allows us to approach a problem from any number of directions." –David Cheresh, Ph.D.

The bad news, of course, is that once you edge past the age of, say, 50, your chances of a heart attack or stroke move up with you. And the vascular leakage phenomenon turns deadly.

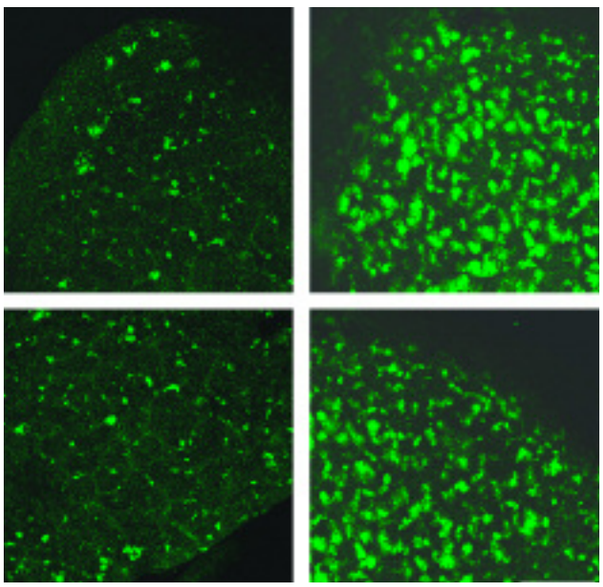
"In a heart attack or stroke, the result is edema, a general term for the swelling caused by a build up of excess fluid in the tissues, and the brain and heart tissue are particularly sensitive to edema," Cheresh says. "In fact, by the time the patient is in the hospital, leakage has begun, and that causes a whole series of events to take place in response."

And none of them are good for you.

"It is something of a vicious cycle," he says. "Vascular leakage causes edema, which in turn causes water accumulation in the cardiac tissue, and that results in the rapid death of cardiac cells. Then, the body tries to close the openings created by the leak response with blood platelets—the coagulation process—so the patient quickly develops a platelet blockage in various micro blood vessels. This blockage results in an inflammatory response that creates more problems including even more vascular leakage. A cascade that begins with a lack of tissue oxygen because of a blocked blood vessel quickly spirals out of control, ending with a growing area of dying or dead tissue within the vessels and the heart itself. The consequences of this cascade are extremely detrimental to healthy long-term heart function."

PROMISING RESULTS

What Cheresh and his laboratory colleagues discovered was that vascular permeability can be selectively controlled by using certain highly specific kinase inhibitors. These inhibitors disrupt endothelial enzymes (kinases) that transmit biochemical and biological information into and through the endothelial cell that allow the cell to respond to its environment. In an article published in the *Journal of Clinical Investigation* early in 2004, Cheresh and his colleagues demonstrated a remarkable reduction of edema-induced tissue injury and increased chances of survival using Src-kinase inhibitors on heart attack models in mice.



Tumor cells expressing the growth factor VEGF (right panels) show enhanced metastasis. Scripps Research investigators are using this type of data to find potential strategies for developing new therapies. *(Reproduced from The Journal of Cell Biology, 2004, Vol. 167(2), pgs. 225 & 226, by copyright permission of The Rockefeller University Press.)*

Their findings were striking.

Mice born without the ability to produce Src-kinase showed no leak response following ischemic injury. Cheresh and his colleague Research Associate Sara Weis, Ph.D., were able to show that in these Src-deficient mice a significant amount—some 60 percent—of the heart muscle following a heart attack was preserved compared with heart attack models in genetically normal animals. So far, specific inhibitors of this molecular pathway have been tested in pigs, rats, and mice with the same results and virtually no toxicity, an important therapeutic factor. If duplicated in human trials, these results could mean more patients would survive heart attacks, and survive in far better condition, than ever before.

One of these agents is now being tested clinically by TargeGen Inc., a San Diego-based biopharmaceutical

company. Based on Cheresh's research and other preclinical efficacy and safety studies, TargeGen is running a combined Phase I/II human clinical trial for patients undergoing an acute myocardial infarction, hoping to transform his initial research into practical human therapies.

Cheresh and his colleagues arrived at the heart attack model by first studying the problem of vascular leakage in stroke; his work on the subject was first published in *Nature Medicine* in 2001. At that time, Robert Paul, a German M.D. and neurologist postdoctoral fellow in Cheresh's lab, suggested that it would be a tremendous medical benefit if the leak response could be controlled in his own stroke patients. If stroke patients were responding poorly to vascular leakage, then the animals without the leak response ability should respond much better. That turned out to be precisely the case.

After the paper was published, Jeffrey Isner, a leading cardiologist, suggested the same implications for myocardial infarction. Sadly, during subsequent studies Isner himself had a heart attack and died. A week after his death, study results showed that the myocardial infarction model worked precisely as predicted. Cheresh and his colleagues had uncovered a common feature of ischemic disease and injury, one that was critical in terms of the outcome of these events.

"Isner was a genuinely inspirational figure," Cheresh says. "His death was a real tragedy and saddened me deeply, but it really brought the idea home that we needed to continue pushing our [myocardial infarction] studies."

FULL CIRCLE

Cheresh is now applying these findings to oncology, his first field of study, trying to unravel the role the signaling pathway (and vascular permeability) plays in the metastatic spread of cancer. By understanding the leak response in endothelial cells, Cheresh has uncovered a parallel response in epithelial cells—the same pathway and the same molecular event that occur in breakdown of endothelial cells are also present in cancerous epithelial cells. Tumor cells have the ability to disrupt their cell-cell junctions in order to establish the cell matrix adhesions necessary for cell invasion.

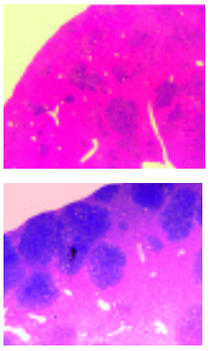
"With our most recent work, we're looking to stop metastatic tumor cells from invading the rest of the body," he says. "Because if they are contained in the blood stream the immune system kills them. By stabilizing the barrier function of the endothelial cells, we can actually keep cancer from metastasizing and reaching other organs."

In the mice with no leak response, tumor cells have a hard time moving past the vascular barrier. In fact, Weis went on to demonstrate that Src-kinase deficient mice don't get metastatic disease at all. Even when the tumor produces its own growth factor, cancer cells are still unable to move out of the blood stream. So far, Cheresh and Weis have seen this response in both lung and colon cancer in mice.

"We've introduced tumor cells into the mouse bloodstream and they failed to get out of the bloodstream with both genetic and pharmaceutical treatment," he says. "What we see down the road is the potential to treat patients in a prolonged way to stabilize the endothelial barrier and to reduce the propensity for cancer cells to move to distant sites. Metastasis is an inefficient process. Anything you can do to tip the balance in favor of the patient may result in a positive outcome."

Cheresh has now come full circle, starting first with his work in tumor angiogenesis, then permeability in stroke and myocardial infarction, and now developing this startling link between cancer and endothelial barrier function. Despite its potential, he makes clear that this is not a cure.

"By stabilizing the endothelial barrier, we're not attacking cancer directly," he says. "We're enhancing the barrier function and helping the patient to resist metastatic disease. You can do it genetically or pharmaceutically, but it's still chronic therapy for a chronic condition."



In contrast to normal (top), models lacking Src-kinase (bottom) are protected from metastasis, the process by which cancer cells can take root in locations in the body far from the original tumor. *(Reproduced from The Journal of Cell Biology, 2004, Vol. 167(2), pgs. 225 & 226, by copyright permission of The Rockefeller University Press.)*

"With our most recent work, we're looking to stop metastatic tumor cells from invading the rest of the body. Because if they are contained in the blood stream the immune system kills them." –David Cheresh, Ph.D.

If this discovery proves successful in the clinic, it would be a contribution of major therapeutic potential. But then Cheresh has always focused on adding value to the fundamentals of scientific research.

"Our primary objective has always been to discover how these inhibitors work at the molecular level. Then, we publish our work, adding our contribution and understanding to what is a large and growing body of important scientific literature."

•*Eric Sauter*

Lower left illustration, "Endangered Tecate Cypress" by Julie Schneider. Native American Indian photography from Smithsonian Institution, National Anthropological Archive.

At the Roots of Alcoholism

CINDY EHLERS FINDS MOLECULAR ANSWERS TO AN URGENT SOCIAL PROBLEM

Some questions have to be asked more than once before they can be answered.

Why are alcoholism and the myriad social and health problems it engenders more prevalent among some populations than among others? And why are the rates of alcoholism so high among American Indians in particular?

"American Indians, in general, have the highest rates of alcoholism [among any group]," says Cindy Ehlers, Ph.D., who is an associate professor in the Department of Neuropharmacology at The Scripps Research Institute. "It's a problem of epidemic proportions."

The numbers are stark. According to Ehlers' own research with a select group of American Indians in California, the lifetime prevalence of alcohol dependence is as high as 72 percent in men and 53 percent in women, compared to an overall U.S. rate of about ten percent in men and five percent in women.

Cirrhosis of the liver is four times higher in American Indians, and alcohol-related mortality is severe; for instance, American Indians have quadruple the normal motor vehicle mortality rate. In fact, they have the highest rates of alcohol-related deaths.

The Indian Health Services, a federal agency within the U.S. Department of Health and Human Services, estimates that three-quarters of all American Indian deaths are related to alcohol, and the agency has cited alcohol dependence as the most urgent health problem facing American Indians today.

The question remains: Why?

In the laboratory, Ehlers and her colleagues in the Scripps Research Department of Neuropharmacology have been trying to uncover the mechanisms and neurobiology of alcohol in the brain. Ehlers studies topics such as the molecular basis for intoxication—a difficult subject given that alcohol does not act upon one single receptor in the brain, but rather on a number of receptors on neurons all over the brain.

But Ehlers' research also has a clinical side. She has been looking to address the problems related to alcoholism among American Indians and has worked for nearly a decade with a number of individuals belonging to several tribes in San Diego County.

Associate Professor Cindy Ehlers, Ph.D., seeks to uncover the mechanisms and neurobiology of alcohol on the brain.

THE PEOPLE

The American Indians in San Diego County are actually several distinct bands that inhabit land in the mountains and river valleys in northern and eastern San Diego County, including the Diegueño People, the Luiseño People, the Kumeyaay Nation, and the Cupeño and Cahuilla Indians. These American Indians were once called "the people," and were dubbed "Mission" Indians by anthropologists because they are regionally associated with the historic San Diego and San Luis Rey Missions in Southern California.

About a decade ago, Ehlers began working with San Diego County Indians to study the alcoholism in their communities.

The study has taken place at Scripps Research's General Clinical Research Center (GCRC), a specialized clinical research unit dedicated to the development of better treatment methods through the careful study of human disease. The GCRC is funded by a grant from the National Institutes of Health (NIH) and is supplemented by donations by the William Black family and the Stein Endowment Fund. Ehlers' study is also funded by the National Institute of Alcohol →

Abuse and Alcoholism and by the NIH Center for Health Disparities.

Approval to conduct the research was granted by the Indian Health Council, an organization with representatives from several Indian bands. And Ehlers is assisted by tribal elders, who have driven individuals involved in the study back and forth to the GCRC from the reservations for the past decade. "They are aware of what I am doing," says Ehlers. "And I go back regularly and talk to them about the results."

Ehlers' clinical work involves both a long-term study of the risk factors that exist for children and a large genetic analysis of adults to determine the factors that contribute to the high rates of alcoholism.

These factors may be psychological, social, biological, or all three, says Ehlers. However, she adds, "Most people in the past have focused on the psychological aspects."

"American Indians, in general, have the highest rates of alcoholism [among any group]. It's a problem of epidemic proportions." –Cindy Ehlers, Ph.D.

IS ALCOHOLISM RELATED TO CHANGING CULTURE?

Focus on the psychological aspects of alcoholism as it relates to American Indians has provided some answers, but perhaps not all the best ones.

One theory that gained popularity a few years ago was that American Indians drink to treat their depression, which is linked to social phenomena including poverty, lack of educational opportunities, high crime, and the stress of losing traditional customs and values and of having to adopt new cultural norms. The rationale behind this theory is reasonable, since depression is linked to alcoholism.

"Unfortunately," says Ehlers, "there is no evidence for the theory. Alcoholism is not associated with increases in depression or anxiety in our study."

In fact, Ehlers published a paper this year in which she found that southwest California Indians had no higher rates of the common psychiatric conditions of depression, bipolar disorder, and schizophrenia than the general population.

"If anything, they have less depression," she says, which is exactly why some questions must be asked more than once.

DOUSING THE FIREWATER MYTH

Another answer some have posited to explain the high rate of alcoholism among American Indians is that they have problems metabolizing alcohol.

"It's part of the firewater myth," says Ehlers.

The firewater myth, now largely discredited by the results of studies conducted by Ehlers and others, basically says that American Indians are more susceptible to the acute effects of alcohol—it makes them really drunk.

Such a phenomenon would not be unprecedented. About 40 percent of people of East Asian descent have a genetic marker, called a "polymorphism" in the language of genomics, in one of the enzymes responsible for metabolizing alcohol.

"[In this case] it looks like what happens is that you feel more drunk and [experience] more of the negative aspects of feeling drunk," says Ehlers.

However, carrying this polymorphism makes one less likely to become an alcoholic, not more, because of the severe negative reinforcement that accompanies drinking. This is borne out by statistics that show low prevalence of alcoholism among East Asians.

There are other genetic polymorphisms unrelated to the metabolism of alcohol that are also protective factors against the development of alcoholism, some of which have been discovered by Ehlers and her Scripps Research colleagues.

In order to address whether certain American Indians carried these same polymorphisms, Ehlers conducted another study. This year, she published her findings that only a small portion of the American Indians in her sample have polymorphisms that protect them against developing alcoholism.

In fact, in results with important implications, the study found most American Indians have a less, not more, intense reaction to alcohol.

"We believe that there is a genetic factor that allows them to drink large amounts of alcohol without feeling intoxicated, and that's one of the factors that leads to a high risk of developing alcohol dependence," she says. However, since this trait is also found in non-Indian sons of alcoholics, it is not specific to Indian people.

THE CLINICAL COURSE OF ALCOHOLISM

Ehlers' research has led her to believe that alcohol dependence is in part heritable, and the basis of inheritance is genes passed to children from their parents.

Ehlers and her colleagues are looking for these genes. They recently did a genome scan, looking broadly across the DNA of large families in order to find markers in the DNA that may be linked to a susceptibility to alcoholism. They are now attempting to map these markers to a particular gene and to a physiological phenomenon, such as alcohol craving and the

experience of alcohol withdrawal, and behavior patterns such as binge drinking.

In order to link biology to behavior, the researchers studied the clinical course of alcoholism among southwest California Indians by asking the individuals to answer some 100 questions about their drinking and use of alcohol. The answers were then analyzed based on standard psychiatric criteria to chart the clinical course of alcoholism in the population. The clinical course is a series of milestone behaviors and events that mark the life of an alcoholic—the progression, over several years, from first drunken bout to alcoholism.

A few years ago, a researcher named Robert Cloninger at Washington University developed a theory based on adoption studies conducted in Sweden that there are generally two types of alcoholism. Type I, marked by a later onset, is environmentally influenced and can be accompanied by depression and anxiety. Type II, which is more genetically mediated, is marked by an early onset and can be associated with antisocial behavior. Ehlers reports that, using this categorization, the American Indians in her studies who have alcoholism generally have Type II alcoholism.

What is different about alcoholism among the American Indians in southwest California, however, is that the course occurs more rapidly—in half the time—something Ehlers refers to as telescoping. The age of onset of a clinical course to alcoholism is earlier (around 20 years of age) and the time of progression from drinking to alcoholism more rapid (six years).

She also noticed a higher rate of some problems, such as drunk driving arrests, fights, and certain health problems. Only 28 percent of the American Indians in the study who suffered from alcoholism sought professional treatment.

Ehlers is looking for environmental variables that may be involved, asking the individuals in the study questions about their education, family, and work.

She also turns to her DNA analyses.

"There are some genes," she says "that are going to help to predict the severity of drinking."

Ehlers and her colleagues found a few DNA sites on chromosomes 4, 15, and 16 that are related to alcoholism. Significantly, some of these sites were also identified in another study that looked at the genetic basis of alcoholism in a population of individuals who were mostly of European descent. This suggests that there are some genetic risk factors that are common across ethnic groups.

They also found sites on human chromosomes 6 and 12 that are related to severity of drinking problems but do not overlap with the other study. Perhaps, says Ehlers, there is a gene or genes at these sites that confer risk more specifically for American Indian alcoholism.

The researchers are now in the process of conducting what is called an association study to identify the genes and to test to see if they are indeed related to risk of alcoholism. The end goal, she says, is to come up with strategies for targeting these genes—perhaps developing new drugs that could help with treatment.

The end goal of the lab's research is to create strategies for targeting genes that confer risk for alcoholism—perhaps developing new drugs that could help with treatment.

CHANGING SOCIAL NORMS

The goal of all Ehlers' research is not simply to understand alcoholism in general and the high prevalence of alcoholism among American Indians in particular. Ehlers' goal is also to turn the research into practical applications to help alleviate the problem of alcoholism.

One conclusion she has reached, for instance, is directly informed by her findings that many American Indians in San Diego County begin down the road of alcoholism at a young age. This suggests a possible intervention strategy.

"It looks like alcohol is more addicting the younger you are, and it also looks like it has more neurotoxic effects [at younger ages]," she says. "We need to target 13 to 15-year-olds and try to delay the onset of drinking," says Ehlers. "By doing that, you may pass over the largest age of risk for addiction."

Another intriguing finding from her studies is that there is a high incidence of what is called "aging out" where individuals stop drinking at a certain age, continuing with their life free of the symptoms of alcoholism. "They go on not to drink anymore," says Ehlers.

"It looks like alcohol is more addicting the younger you are, and it also looks like it has more neurotoxic effects [at younger ages]. We need to target 13 to 15-year-olds and try to delay the onset of drinking. By doing that, you may pass over the largest age of risk for addiction." –Cindy Ehlers, Ph.D.

This seems to occur around the time an individual reaches the age of 40 and coincides with life changes, such as an increase in work and family responsibility.

"We need to find out from individuals what are the common things that contribute to the aging out process and build those into the treatment programs," she says.

That is a good question for another day.

•Jason Socrates Bardi

Focus on Florida

SCRIPPS FLORIDA INTRODUCES INNOVATIVE PROGRAMS AND RECRUITS WORLD-CLASS SCIENTISTS

The Scripps Research Institute launched several innovative research programs in 2004 at its Scripps Florida facility in Palm Beach County.

The new programs indicate the depth and scope of the scientific research planned at Scripps Florida. They include developing cutting-edge technologies to enable scientists to examine the basic biology of human health and applying those technologies to find new and better treatments for a variety of devastating human diseases.

"Scripps Florida's scientific programs are uniquely geared to answer some of the most important questions in biology and medicine," says Richard A. Lerner, M.D., president of The Scripps Research Institute, where he is also the Lita Annenberg Hazen Professor of Immunochemistry and holds the Cecil H. and Ida M. Green Chair in Chemistry. "Our researchers will be addressing diseases such as AIDS, cancer, diabetes, obesity, mad cow disease, Parkinson's, and schizophrenia, to name just a few."

A number of highly accomplished and acclaimed scientists have been recruited to carry out much of the research in these new programs at Scripps Florida.

"Scripps Florida's scientific programs are uniquely geared to answer some of the most important questions in biology and medicine." –Richard A. Lerner, M.D.

THE NEW RESEARCH PROGRAMS

The Genetic Disease Informatics Program will seek to manage and mine the wealth of scientific data generated over the last decade from massive projects such as the Human Genome Project. The research will employ human and model organism genetics and genomics data to derive networks of interacting genes in order to identify key intervention points that will aid in the discovery of novel human therapeutics. These networks will include genes that undergo "alternative splicing," where a single DNA gene might produce a variety of RNA transcripts, each encoding a different protein. Some of these differences may account for different disease states, including inflammatory and metabolic diseases.

Nikos Tsinoremas (Ph.D., University of Leeds, England) will lead the program. Tsinoremas has worked for a number of leading biotechnology companies, serving most recently as director of Computational Genomics and Genomic Discovery at Rosetta/Merck in Seattle, Washington.

The Genetics of Complex Diseases Program will seek to study known genes and to identify unknown genes that affect behavior, particularly learning and memory. It will address how multiple genes work together to affect behavioral functions and how variations in these gene sequences contribute to late-onset diseases, such as bipolar disorder and schizophrenia.

The Cancer Biology Program will focus on the cell cycle, the essential biological process whereby cells divide. Researchers will look for ways to understand and address the health problems that arise when cells lose their ability to divide, are injured (such as in traumatic head injuries), or divide too much (such as in cancer).

The Infectology Department Program is focusing on prion diseases (spongiform encephalopathies, such as mad cow disease and its human cousin, variant Creutzfeld-Jakob disease). Investigators are studying the nature and components of infectious prions, asking such questions as how prions are transmitted from cell to cell and which genes contribute to susceptibility or resistance to prion infections.

Preeminent Scripps Florida scientist Charles Weissmann (M.D., Ph.D., Zurich University) heads the Infectology Department. Weissmann comes to Scripps Florida from University College, London, and is widely recognized as a pioneer in modern biomedical research.

The Proteomics Program will focus on developing and applying advanced technologies in mass spectrometry-based proteomics. Proteomics is the field that examines the expression and action of the gene products (proteins) in different cell types and states, and the Proteomics Program will focus on such questions as how proteins are modified by cells in certain diseases.

The Nuclear Hormone Receptors Program will look at how drugs and other chemicals bind to human proteins called nuclear hormone receptors—a broad class of cellular receptors involved in diabetes and a number of other diseases. Investigators in the program will aim to understand how nuclear hormone receptors interact with the chemicals that bind to them, hoping to understand the mechanism of action of these proteins and determine how they are involved in processes like inflammation and insulin resistance. They will also aim to develop rapid assays to study the three-dimensional interactions of nuclear hormone receptors with any number of chemicals so that these chemicals can be quickly screened for their potential as candidates for new anti-inflammatory drugs and better drugs for Type 2 diabetes.

Patrick Griffin (Ph.D., University of Virginia), who comes to Scripps Florida from ExSAR Corporation in Monmouth Junction, New Jersey, will lead the Nuclear Hormone Receptors Program.

The Drug Metabolism and Pharmacokinetics Program will provide many of the other research programs with the tools needed to support the development of new drugs. Drug metabolism and pharmacokinetics make up a broad area important to drug research that looks at such factors as how soluble and stable a drug candidate is, how rapidly a potential drug is cleared from the body, how a potential drug interacts with enzymes in the intestines and liver, and how well a drug candidate crosses the blood-brain barrier.

Griffin, who leads the Nuclear Hormone Receptors Program, will also be heading this research program.

The Diabetes and Obesity Program will combine functional neuroanatomy with genetics to focus on the neural circuits and chemicals in the brain that underlie changes in appetite and metabolism. This program includes studies of these circuitries in both health and disease (infection or chronic illness).

Teresa Reyes (Ph.D., University of Wisconsin), who comes to Scripps Florida after completing advanced postdoctoral studies at the Salk Institute for Biological Studies in La Jolla, will lead the Diabetes and Obesity Program.

The Medicinal Chemistry Program will be generating compounds to test for activity against diseases such as cancer and arthritis.

The programs at Scripps Florida (rendering of the planned campus shown here) will include the development of cutting-edge technologies to enable scientists to examine the basic biology of human health and to find new and better treatments for diseases. *(Courtesy of Zeidler Partnership/Bohlin Cywinski Jackson.)*

Noted chemist William Roush (Ph.D., University of California, Los Angeles) will lead this program. Roush was previously chair of the University of Michigan, Ann Arbor, Chemistry Department and Warner Lambert/Parke Davis Professor of Chemistry, where he performed groundbreaking research in the analysis, structure determination, and synthesis of complex, biologically active natural products.

The Cell-based Screening Program will develop and apply assays that allow scientists to systematically evaluate gene function and the effects of small molecules in living cells, thereby providing a baseline of annotation of gene function as well as providing useful chemical probes for understanding important cellular pathways. These technologies will be integrated with other technologies such as informatics, RNA expression dynamics, genetics, and proteomics to select promising disease or pathway targets for further study.

John Hogenesch (Ph.D., Northwestern University), associate professor and head of Genome Technology at Scripps Florida, will lead the Cell-Based Screening Program. Previously, he served as head of genomics at the Genomics Institute of the Novartis Research Foundation and assistant professor of neuropharmacology at Scripps Research in La Jolla.

The HIV Therapeutics Program will be geared toward designing synthetic peptide-based inhibitors against pathogens, such as human immunodeficiency virus (HIV), which prevent the virus from replicating.

James Tam (Ph.D., University of Wisconsin, Madison), will head the HIV Therapeutics Program after more than a decade as a distinguished chemist and professor in Vanderbilt University's Department of Microbiology, Immunology, and Biochemistry in Nashville, Tennessee.

Interview with Harry Orf

SCRIPPS FLORIDA

Harry W. Orf, Ph.D., Scripps Florida vice president of scientific operations.

Endeavor *spoke recently with Harry W. Orf, Ph.D., Scripps Florida's new vice president of scientific operations, about his background, management philosophy, and plans for the Scripps Research facility in Palm Beach County. Orf has held positions including director of the Molecular Biology Laboratories at Massachusetts General Hospital, principal associate in genetics with Harvard Medical School, founder and principal of Cambridge Laboratory Consultants, Inc. and Nexus Cambridge Lexington LLC, and colonel with the U.S. Army's 804th Medical Brigade.*

ENDEAVOR> I understand you recently returned from a tour of duty in Iraq and Kuwait. When did you get back?

ORF> We were there from February '03 to February '04. In Iraq, we controlled all the medical assets in our half of the theater—the hospitals, medical supplies, blood, preventive medicine teams, veterinary services, medical logistics, dental units, surgical teams, etc. It was a pretty interesting year—a lot different than training once a year.

ENDEAVOR> Were you in the reserves a long time?

ORF> Thirty-three years. I joined during the Vietnam War. The story is that when the draft lottery was held, I got a high number—16—which meant that I was almost certainly going to be subject to the draft.

The problem was I had just been accepted for graduate school with Harvard University's Chemistry Department. I said to the people at Harvard, "If I get drafted, I'll be gone two, two-and-a-half years. Can I come back then?" And they said, "No, you'll have to reapply, and frankly, if you've been away from chemistry, you probably won't get in."

So I called my draft board and said, "I've just been accepted for graduate school at Harvard, and they only defer admission one year." I was told, "Well, there's nothing you can do unless between now and three weeks from now when you graduate, you can find a reserve unit to get into."

A few blocks away from where I lived, I had noticed a door that said "Army Reserve." I went in and said I wanted to sign up. The guy started laughing. He said, "Look, this is a general hospital." I had walked into a general hospital and didn't even know it. "We have two openings here. The opening that everybody signs up for is a medic, but I've got 600 people ahead of you, and there's not a chance that you'll be called for another year. The other opening is for a lab tech. But you need a degree in chemistry to get in that program." I was so excited I started jumping up and down. At first, he didn't believe I had the degree, but I brought in a transcript, and he swore me in the next week.

There were some pretty extraordinary people in the service. In the end, I stayed with the reserves. It's been engaging and interesting. Over the years, we've done a lot of great humanitarian missions, such as helping to provide medical care in Central America and Eastern Europe.

ENDEAVOR> What kind of chemistry did you do at Harvard?

ORF> Organic chemistry. I did my thesis with E.J. Corey, who received the Nobel Prize in Chemistry in 1990.

ENDEAVOR> E.J. Corey is well-known at Scripps Research, since K.C. Nicolau is on our faculty.

ORF> Yes, K.C. and I were in the Corey lab together. He worked for E.J. as a postdoc when I was a graduate student. We were right across the hall from each other.

ENDEAVOR> Was it a conscious decision to move out of science and into management?

ORF> My work in the lab was in computers and chemistry, and it was very interesting. What got me going in the direction of administration was the three years I spent as academic dean while I was a postdoc, dealing with 550 students in a college dorm. I really

enjoyed the personal interaction. I enjoyed problem solving on a practical basis.

As I was getting ready to leave Harvard, I was hired to be director of a brand-new department there, Biochemistry and Molecular Biology. I had full management responsibility for the department, which grew to about 250 people, including a dozen research faculty with varying size groups, and staff in such areas as purchasing, accounting, facilities management, and animal care. I found the experience of building a new department, staffing it, and helping hundreds of people do their science as rewarding as lab work.

So I let myself get pulled in that direction, and I eventually phased out of research into administration.

ENDEAVOR> What led you to the directorship of the Molecular Biology Laboratories at Massachusetts General Hospital?

ORF> My colleague, the associate director of the Chemistry Department, became my business partner. Biotech was starting up around this time, and we were asked by many colleagues to help form new companies and get them going. Massachusetts General asked our company to help design a new building for its Molecular Biology Department. That job led to the directorship.

ENDEAVOR> Did all these experiences give you a particular management philosophy?

ORF> I think I've learned something from each of them.

First is that when you get to a level of responsibility above middle management it's a mistake to micromanage. Instead, what you need to do is to surround yourself with good people who share your philosophy of teamwork and management and whom you can trust, and then give them explicit guidelines, make it clear what you expect, and then let them do it. I've had the opportunity to observe generals who micromanaged and those who didn't. In academic circles and in hospitals, micromanaging can also be a problem. But good managers need to step back and let their people do the work.

Secondly, you want everybody to feel part of a team. Everyone should know and understand what everybody else does in the organization. In contrast, the Army has a philosophy called "stay in your lane," which, at its best, means focus on your area of expertise, and don't try to tell other people what to do. But unfortunately, it's often interpreted as, "If it isn't exactly what I'm responsible for, it's not my problem." And that's the antithesis of what you want in a staff. The most important thing we can do in Florida is to give the staff we're going to build a sense that we are a team. That's the philosophy we hope to instill.

ENDEAVOR> What other goals do you have for Florida?

ORF> On the way to La Jolla, I was writing a speech about what I want to do in Florida called, "Looking West, Looking Forward."

As for looking West, I think we need to build on the tremendous success that Scripps Research has in La Jolla. We've got a terrifically successful organization, scientifically and administratively. We want to leverage the key people and their experience. While we're building the staff up in Florida, we have the advantage of having all those experts in California, able to help us get things done.

In terms of looking forward, we need to take advantage of the fact we're smaller than the Scripps parent. We can be a test bed for innovation—electronic paperless purchasing, as an example.

ENDEAVOR> Why did you take the job?

ORF> Interesting question. The initial talks about the position started when I was still in Iraq, right before we left. I had been away from my department for a year. The department had been running without me, thanks to some very good people. Two of my kids are out on their own. My second wife and I have a two-and-a-half-year-old son, who doesn't have educational or schooling issues yet. So the timing was good in terms of my family life.

Having said that, initially, I didn't think anything would come of it. I had been at Harvard for 30 years and Massachusetts General for 20 of those, and I was not looking to relocate or to change. But the enthusiasm that I saw and the quality of people I encountered made a huge impression on me. And the chance to build an institution on this scale simply would not have come along again. It is truly a unique opportunity.

•Mika Ono Benedyk and Jason Socrates Bardi

Letter from the Development Committee Chair

Ralph Shapiro and his wife Shirley, Los Angeles-area philanthropists, are part of Scripps Research's new philanthropic leadership.

Dear Friends:

As the new chairman of The Scripps Research Institute's development committee, it is my pleasure to highlight three significant changes in the life of our institution that occurred during the past year and to report on results in fundraising these changes helped make possible.

CHANGES:

(1) In January 2004, Scripps Florida became a reality with the signing of an agreement between Scripps Research and the State of Florida. At the same time, Scripps Research opened an office of external affairs in West Palm Beach as Scripps Florida's fundraising arm, naming Dr. William E. Ray, for 22 years CEO of the Palm Beach County Cultural Council, as director of external affairs. Alexander W. Dreyfoos, founding chairman of the Raymond F. Kravis Center for the Performing Arts in West Palm Beach, was named to the Scripps Research board.

(2) In April 2004, Scripps Research entered into a formal agreement with Scripps Health to dissolve the Scripps Foundation for Medicine and Science—the entity created in 1993 to carry out joint fundraising for Scripps Research and Scripps Health—making Scripps Research fundraising fully independent from Scripps Health. At the same time, Scripps Research began the process of expanding its California fundraising staff under Denise M. Scalzo, director of development, to take over fundraising tasks formally carried out for Scripps Research by the foundation.

(3) In July 2004, California and Florida fundraising operations were merged into a single, seamless entity, with Denise and Will made vice presidents, reporting to Dr. Richard A. Lerner and Douglas A. Bingham—a reflection of the importance placed by Scripps Research on a national fundraising effort. As a direct result, fundraising staff is being increased in California and Florida. Members of the board from Florida were added to the development committee to further strengthen the institute's new national fundraising platform. →

RESULTS:

(1) Funds raised from private sources by the Scripps Research Development Office increased from over $21 million in FY '03 to almost $28 million in FY '04, with $25.7 million coming in gifts and pledges from California and $2.2 million from Florida. Even without Florida, this represents a 17 percent increase in private philanthropy.

(2) One-half of the total raised last year came from two sources. The Skaggs Institute Foundation contributed $9.7 million toward the Sam and Aline Skaggs family's extraordinary 10-year pledge of $100 million, while a new contribution of $3 million to create the Pearson Center for Alcoholism and Addiction Research confirmed that Scripps Research can increase its share of major gifts in the highly competitive philanthropic market.

(3) Within 90 days of the opening of Florida development operations, two million-dollar pledges to Scripps Research were announced there: one to create the Office Depot Program in Childhood Neurodegenerative Diseases in Florida, the other—from Elizabeth Fago, a gubernatorial appointee to the state's Scripps Research funding oversight board—to support Dr. Jeffery Kelly's research on Alzheimer's disease in California. An additional $150,000 came in amounts of $5,000 or more from Florida donors as unrestricted gifts to Scripps Research operations.

This experience confirms three things, all good for Scripps Research's future.

First, the decision to extend operations into Florida opens an eastern fundraising frontier that will make Scripps Research even more competitive in the international circle of independent biomedical research institutions. Second, the decision to separate from Scripps Health in fundraising will make Scripps Research stronger by building independent capacity in critical areas such as donor research and records, development marketing, and planned giving. Finally, integration of fundraising activities in California and Florida, along with restricted and unrestricted giving to California from Florida, adds a dimension to the institute's development profile and dollars to its bottom line.

Sincerely yours,

Ralph J. Shapiro
Chairman, Development Committee

Development Report

MAJOR DONORS TO THE SCRIPPS RESEARCH INSTITUTE

The Scripps Research Institute depends on the generosity of its many friends to deliver cutting-edge basic biomedical research work and breakthrough scientific discoveries. We are extremely grateful for your generosity. Your contributions help build a foundation of knowledge that will have a profound impact on humankind for generations to come.

On the following pages, we recognize those who have supported our research this year to prevent and cure disease. We give special recognition in sidebars to a few of the people and organizations who have shown how private philanthropy advances the work of Scripps Research scientists and educational and community programs. (Names in italics indicate Scripps Research faculty and staff.)

SPECIAL ACKNOWLEDGEMENT FOR LIFETIME GIFTS

The following are those individuals and organizations, who, over the years, have given $1 million or more to the research institute. They deserve special recognition for their dedication to the advancement of science.

Anonymous (9)
Aline W. and L. S. Skaggs/
The ALSAM Foundation/
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Dr. Andrew and Erna Viterbi

THE SCRIPPS LEGACY SOCIETY

The Scripps Legacy Society is composed of individuals who have included Scripps Research as a beneficiary in their estate plans.

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Mrs. Nena-Joy Almodovar
Gordon and Rita Archibald
Mike and Stella Banich
Mr. Bruce G. Barnes
Mr. and Mrs. Michael J. Buckley
David S. and Pamela M. Carton
Mrs. Grace Caton
Mr. Stanley Corbin
Mabel I. Danenberg

GRADUATE EDUCATION

***Janet ("Jean") R. Kellogg and W. Keith Kellogg II* have made extraordinary contributions to science and education for many years. As a result of their commitment to graduate education, Scripps Research has named its graduate college the Kellogg School of Science and Technology. The Kelloggs' generous support has resulted in the recognition of the graduate program as one of the most respected in the country. Their continuous support of the graduate program ensures excellence in education and innovation. Their impact will be felt for generations as these scientists mature and contribute to society.**

TRADITION

***Claudia Skaggs Luttrell* is continuing the tradition her family established at Scripps Research by serving as the new president of The Skaggs Institute for Research. Her belief in the potential of the Skaggs Institute to advance science is demonstrated by her dedication to this remarkable institution, which captures the thrill of discovery in biology and the ingenuity of invention in chemistry, ultimately leading to the relief of human suffering through better medicine.**

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OCTOBER 1, 2003 TO SEPTEMBER 30, 2004

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LEGACY

For more than a decade, *John and Becky Moores* have been among the most generous philanthropists in the world, supporting a variety of causes around the globe. They have given $18 million to Scripps Research and were instrumental in establishing the campus's Institute for Childhood and Neglected Diseases. Currently, John Moores is chairman of the San Diego Padres Baseball Club, chair of the University of California Board of Regents, and a member of the Scripps Research Board of Trustees.

IN MEMORIAM

The science and philanthropy of *Arnold O. Beckman*, Ph.D., left a lasting legacy at the Scripps Research campus, as it did for American science, business, and education. The Arnold and Mabel Beckman Foundation provided major support for the Arnold and Mabel Beckman Center for Chemical Sciences, a building that opened in 1996 on the Scripps Research campus. Today, the Beckman Center houses more than 400 scientists. By the time he celebrated his 100th birthday, Arnold Beckman had given more than $270 million to support scientific research worldwide. He will be missed.

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The brothers *Charles, Robert, and Sam Scripps*—nephews of Ellen Browning Scripps, who founded Scripps 80 years ago—have continued the family's legacy. Over the years, the brothers have provided major financial support for buildings, programs, and operations at Scripps Research, including its Institute for Childhood and Neglected Diseases and the Arnold and Mabel Beckman Center for Chemical Sciences. The brothers are true friends of Scripps Research.

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We have done our best to make this list an accurate reflection of gifts to Scripps Research from October 1, 2003 to September 30, 2004. If errors or omissions exist, please accept our apologies and call us at (858) 784-2037. Thank you, Scripps Research Development Staff.

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, programs generally do not qualify for federal grant support until they are fully developed. Young scientists who have not yet achieved prominence are also at a disadvantage in competing for grants; their search for funds can delay their work and inhibit them from striking out in new directions. As a result, unrestricted gifts constitute one of the most valuable resources for Scripps Research because they 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 1,000 Friends of Science.

THE IMMUNOLOGY DEPARTMENT BUILDING

In 1961, the Department of Experimental Pathology was the cornerstone of the newly established Scripps Clinic and Research Foundation. With the arrival of Frank Dixon Jr., Ph.D., the department began investigations in the fledgling field of immunology that would eventually lead to the creation of The Scripps Research Institute.

In just a few decades, Scripps Research has become a leader in the field of immunology. Its scope of study has grown dramatically, from basic research in the 1960s to groundbreaking investigations into diseases affecting millions of people worldwide—diabetes, cancer, septic shock, Ebola, arthritis, lupus, multiple sclerosis, tuberculosis, hepatitis C, prion disease, and blood disorders such as HIV. At the same time, the department has expanded its work into early clinical development, giving Scripps Research scientists an opportunity to aid patients directly.

Scripps Research has a one-time opportunity to purchase the Immunology Building, the southern anchor to the main campus, at a price below market value. The building, which has been leased by Scripps Research since 1980, houses the Department of Immunology, the institute's oldest and largest department comprising approximately 60 faculty members, 100 research associates, and 340 staff members. For 25 years, the building has housed research unlocking the secrets of the complex human immune system and developing potential treatments for global killers.

A naming gift will assure a donor major 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
East Conference Room	$ 200,000
Laboratory	$ 75,000

INSTITUTE FOR CHILDHOOD AND NEGLECTED DISEASES

The Institute for Childhood and Neglected Diseases at Scripps Research 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 accelerating knowledge of genes to specific childhood and early-onset diseases. For a number of years, researchers have attempted to use gene therapy against many of these diseases—cystic fibrosis, muscular dystrophy, 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 lays the groundwork for approaches that will succeed. In other conditions, such as autism, scientists are uncovering genetic clues that will soon lead to better treatments.

Most 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 Scripps Research's past successes, and will use the latest advances in biology to help vanquish invidious parasitic diseases.

GIVING OPPORTUNITIES Gifts of all sizes are welcome, and 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. A commitment of $75,000 will support a laboratory that will bear the name of the donor or designee.

THE HELEN L. DORRIS CHILD AND ADOLESCENT NEURO-PSYCHIATRIC DISORDER INSTITUTE

The Helen L. Dorris Child and Adolescent Neuro-Psychiatric Disorder Institute was recently established with a generous gift from mental health advocate and San Diego State University professor emerita Helen L. Dorris. Its mission is to uncover the pathological basis of neurological and psychiatric disorders and to pave the way for new therapeutic approaches. Benjamin Cravatt, Ph.D., director of the new institute, leads the effort to recruit an interdisciplinary team of scientists to focus on understanding neuropathology in children and adolescents.

GIVING OPPORTUNITIES Gifts of all sizes are welcome. A commitment of $150,000 will establish a senior research fellowship that supports the work of a senior scientist for two years. A commitment of $75,000 will support a laboratory that will bear the name of the donor or designee.

FACULTY CHAIRS

An endowment gift to establish a named faculty chair at Scripps Research is one of the most meaningful and lasting gifts available to any donor. Such a gift perpetuates philanthropy by creating a permanently funded position, named by or for the donor, which may be occupied in succession by major figures in biomedical science. The benefits will be enjoyed by future generations.

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 designee. 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 of discoveries in basic research are unknown, but build the foundation for 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 may lead to better therapeutics and medical advances. Funding a senior research fellowship is a way to participate in 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 work.

HAROLD L. DORRIS NEUROLOGICAL RESEARCH CENTER

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

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

The center seeks contributions to supplement a founding gift of $10,000,000 in order to recruit additional senior faculty members, 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; a gift of $1,250,000 will endow and name a senior research fellowship; and a gift of $500,000 will establish a visiting professorship. Specific program funding in the range of $50,000 to $300,000 for new scholars provides another way to give.

THE KELLOGG SCHOOL OF SCIENCE AND TECHNOLOGY

With its emphasis on individualized instruction, adherence to the highest scientific standards, and reputation for

research excellence, Scripps Research provides an unparalleled environment for advanced study and outstanding preparation for successful careers in science.

In 1989, Scripps Research established a Ph.D. program in Macromolecular and Cellular Structure and Chemistry. Three years later, a second Ph.D. program in Chemistry was established to focus on synthetic and bioorganic chemistry. In 2003, the institute restructured its programs to provide students with a wide range of courses and increased flexibility in course selection through the renamed Doctoral Programs in Chemical and Biological Sciences. The program provides an exceptional training opportunity in a unique learning environment for a select group of intellectually outstanding students.

In honor of their extraordinary contributions to science and education Scripps Research named its graduate division the Kellogg School of Science and Technology for philanthropists Janet R. ("Jean") Kellogg and W. Keith Kellogg II.

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 $425,000 will endow a graduate student stipend in perpetuity. A commitment of $10,000,000 will permanently endow the graduate program.

EDUCATIONAL OUTREACH PROGRAMS

As one of the world's leading biomedical research institutions, The Scripps Research Institute has made a commitment to science education. Using the institute's intellectual and material resources, the program introduces high school and undergraduate students and middle and high school science teachers to contemporary issues in biomedical research and intensive, hands-on laboratory experiences, encouraging students to pursue careers in the biological and chemical sciences. Scripps Research's Educational Outreach Programs represent a cornerstone of the institute's commitment to training the next generation of scientists.

At this time, Scripps Research can serve up to 50 summer interns. With the demand and popularity of this program in high schools, the main limiting factor is 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 will endow and name the entire program.

ENDOWMENTS

The Scripps Research Institute seeks to enhance its endowment from private contributions for ongoing income to complement federal support. An endowment gift is one of the most meaningful and lasting gifts available to the donor. 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. A gift of $2,000,000 will establish a named faculty chair to be occupied by a dean, director, or department chair. There are other endowment opportunities throughout the institute's departments and centers. Specific programs and needs within the Educational Outreach Programs can be endowed with gifts of $100,000 and up.

EQUIPMENT ACQUISITION

Scripps Research enjoys one of the world's leading private computational capabilities, with an array of computers that includes a Cray supercomputer. Research is 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.

Scripps Research 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 technology are constantly being developed to improve both efficiency and effectiveness. Gifts of discretionary funding are critically important to support the continuous modernization of laboratories at the institute.

GIVING OPPORTUNITIES Gifts of all sizes are welcome.

THE KRESGE LIBRARY

Gifts of discretionary funding are needed to fund the renovation of the Kresge Library. The library's furnishings,

including well-used study carrels and chairs, have served students and faculty since the 1970s and are in need of replacement and repair.

GIVING OPPORTUNITIES Gifts of all sizes are welcome.

GIFTS TO THE SCRIPPS RESEARCH INSTITUTE

Gifts to Scripps Research insure that the institution will continue to achieve excellence in biomedical research. Unrestricted gifts are particularly useful and are applied to 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 may be able to carry over the remaining deduction to succeeding tax years. This means that with careful planning, nearly every outright gift to Scripps Research can be deducted.

GIFTS OF SECURITIES

Giving appreciated stocks or bonds is another way to show support for the institution. You can deduct the full fair market value of long-term appreciated securities and avoid tax on the capital gain. A gift of securities is deductible up to 30 percent of your adjusted gross income, with a five-year carry-over option. Under certain circumstances, 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 to its cost basis.

GIFTS 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 and can be made either outright or through other methods.

If the property has appreciated in value and is given outright, you may avoid 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, but you may deduct the value of the gift up to 30 percent of your adjusted gross income. Under certain circumstances, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation to its cost basis.

GIFTS OF RESIDENCE

Tax laws enable you to donate your personal residence and still live there for the remainder of your life. Furthermore, you can stipulate that your spouse or partner live there for his or 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, but 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.

In these cases, your charitable deduction is less than the full value of the property and equals the value of the remainder interest given to Scripps Research. 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 is given to Scripps Research.

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.

GIFTS BY BARGAIN SALE

This entails transferring ownership of an appreciated asset (real estate, securities, and the like) to Scripps Research. In return, the institute would pay an agreed-upon amount that is less than the full fair market value—usually your original cost. Essentially, you are selling your asset to Scripps Research for less than its fair market value, so the transaction is part gift and part sale.

You might 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 and the full fair market value. You incur tax only on the part of the appreciation attributable to the sale.

GIFTS OF LIFE INSURANCE

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 Scripps Research. There are two ways to do this.

You may make Scripps Research the owner of the policy. This allows you an immediate income tax deduction. If the policy is fully paid, 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 Scripps Research; Scripps Research, in turn, could pay the premiums. As long as the institute is not under any obligation to pay the premiums, your contribution would be fully deductible.

You also may name Scripps Research 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 a 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 Scripps Research.

LIFE INCOME GIFTS

Another way to make a gift to Scripps Research is to transfer property (e.g., cash, securities, real estate) to the management of a trustee (for example, Scripps Research as an independent agent), and establish a life income arrangement. After the lifetimes of the beneficiaries, Scripps Research receives 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 taxes, 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, and gift annuity. Information about each gift arrangement can be obtained from the Development Office at Scripps Research.

GIFTS 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 Scripps Research 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 Scripps Research immediately receives funds for its programs. This arrangement is called a lead trust.

CORPORATE MATCHING GIFT

Many companies encourage philanthropic giving by their employees and 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 human resources office).

GIFTS BY BEQUEST

One of the easiest and most common ways to make a gift to Scripps Research is through a bequest in your will. The tax laws encourage bequests; making a bequest is an excellent way to support the institute's programs. Bequests work particularly well for those who are unable to make an immediate outright gift but would like to aid Scripps Research 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, Scripps Research 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 Scripps Research, 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 when the taxable estate, after other deductions, exceeds the amount offset by individual estate tax credits. Because the estate tax rate schedule is progressive, the larger the taxable estate, the greater the potential tax savings per dollar given.

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

The Scripps Research Institute
Development Office
10550 N. Torrey Pines Rd.
Mail Drop TPC-2
La Jolla, CA 92037

www.scripps.edu

(858) 784-9367
(800) 788-4931
(858) 784-2608 *fax*
hodgins@scripps.edu

With Your Help, We Have a Chance

Throughout its 80-year history, The Scripps Research Institute, one of the largest nonprofit research organizations in the United States, has played an important role in revolutionary breakthroughs in biomedical science. Today, it continues to play a significant part in discovering treatments for disorders such as heart disease, cancer, autoimmune diseases, Alzheimer's, and AIDS.

The internationally ranked research institute, now on two coasts, is making significant advances. Ultimately, its groundbreaking science will lead to the development of new medicines to ease human suffering from debilitating diseases.

Scripps Research employs over 1,000 Ph.D.s and M.D.s in seven departments, all renowned for cross-disciplinary projects and programs. Three Scripps Research faculty members and 11 members of the institute's Scientific Board of Governors are Nobel laureates. The Scripps Research doctoral programs in biology and chemistry, dedicated to training the young scientists of tomorrow, are among the nation's top 10 programs according to *U.S. News and World Report*.

Your gift contributes to excellence in biomedical research and the enhancement of quality of human life, providing hope to friends, family members, and neighbors living with disease.

Many challenges lie ahead: continued support for research is needed to surmount still formidable technological hurdles. Scripps Research depends on private philanthropy to enhance and extend this work in new, often nontraditional directions.

The research advances we make today may save the life of a loved one tomorrow. With your help, we have a better chance.

1,000 Friends of Science

With the opening of Scripps Florida, the dissolution of the Scripps Foundation for Medicine and Science, and the newly independent status of Scripps Research's fundraising efforts, a new group has been formed—"1,000 Friends of Science."

Annual membership in 1,000 Friends of Science is a benefit to acknowledge individuals who contribute $1,000 or more in a given year. Gifts may either be earmarked for specific research purposes or left for use where the need is greatest.

Special privileges are extended to all members of 1,000 Friends of Science:

- A yearly report that outlines the impact of your gift,
- An invitation to the 1,000 Friends of Science 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,
- Selected media releases on topics of general interest which keep members informed about Scripps Research's activities,
- Scripps Research's *Endeavor*, a publication featuring the scientists and scientific progress at the institute. The year-end issue also recognizes Scripps Research supporters.

In addition to recognizing contributions of more than $1,000, we acknowledge annual giving at the following levels:

Founders' Circle: $5,000 - $9,999

President's Circle: $10,000 - $24,999

Chairman's Circle: $25,000 - $49,999

Fellows' Circle: $50,000 - $99,999

Members receive the satisfaction of knowing they have personally contributed to the advancement of biomedical research through their gifts.

If you are interested in joining any of our membership programs, please contact:

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Development Office
10550 N. Torrey Pines Rd.
Mail Drop TPC-2
La Jolla, CA 92037

www.scripps.edu

(858) 784-9367
(800) 788-4931

The Scripps Legacy Society

The Scripps Legacy Society is composed of individuals who have included Scripps Research as a beneficiary in their estate plans. This includes those who have established a Charitable Remainder Trust, Charitable Gift Annuity, or Charitable Lead Trust; have given the remainder interest in their real property; or have named Scripps Research as a beneficiary in their trust, will, or retirement plan.

Benefits include an invitation to the annual Scripps Legacy Society event, recognition in our annual report, and invitations to scientific lectures and gatherings. We would be happy to add your name to the philanthropists listed in our publications or to honor any request to remain anonymous.

For more information about becoming a member of the Scripps Legacy Society, please contact:

Cheryl H. Dean, Esq.
Planned Giving Counsel
The Scripps Research Institute
Development Office
10550 N. Torrey Pines Rd.
Mail Drop TPC-2
La Jolla, CA 92037

www.scripps.edu

(858) 784-2380
(800) 788-4931
(858) 784-2608 *fax*
cdean@scripps.edu

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