

THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR



Breakthroughs of 2005



THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR

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FEATURES:

08 FAT, BRAINS, AND PREGNANCY:

JEROLD CHUN MAKES SOME SURPRISING CONNECTIONS



14 BREATHING EASIER:

HUGH ROSEN'S WORK MAY HELP POTENTIAL VICTIMS OF "SHOCK LUNG"



18 THE PRAGMATIST:

FLOYD ROMESBERG OFFERS A NEW TAKE ON EVOLUTION



ALSO:

01 PRESIDENT'S INTRODUCTION

23 FOCUS ON EDUCATION AND OUTREACH

25 TRIBUTE TO KEITH KELLOGG

28 ZADIG'S LOGIC: COMMENCEMENT 2005

31 LETTER FROM CHAIR OF THE BOARD

33 DEVELOPMENT REPORT

ENDEAVOR IS A PUBLICATION OF *THE SCRIPPS RESEARCH INSTITUTE*

The issue of *Endeavor* magazine features breakthroughs of 2005 at The Scripps Research Institute. Among many significant scientific milestones this year: discoveries related to brain development and infertility, work holding promise for people stricken with acute respiratory distress syndrome (also known as "shock lung"), and new insights into the chemical basis of evolution that may help combat bacterial drug resistance.



Richard A. Lerner, M.D.,
president

Year in Review : 2005

01

PRESIDENT'S INTRODUCTION

At The Scripps Research Institute, 2005 was about many things—innovative research, scientific exchange, and remarkable support from public and private sources. Our new operation in Florida forged ahead in the lab. Our La Jolla faculty built on past successes. And researchers on both coasts came together to work toward our common goal—improving human health and quality of life through science. →

PRESIDENT'S INTRODUCTION

Faces from Florida

TOP: Donny Strosberg, Patrick Griffin, Corinne Lasmezas
BOTTOM: Teresa Reyes, Claes Wahlestedt



*Scripps Florida has attracted
renowned faculty.*



SCRIPPS FLORIDA

A Scientific Hub

Scripps Florida represents a new era for the institute—one that renews our commitment to forward-looking biomedical research, embraces promising technologies in drug discovery, and draws on resources from both coasts to strengthen and energize our institution. Currently, Scripps Research scientists are operating out of temporary space on the campus of Florida Atlantic University in Jupiter. The first building, completed in March, will be augmented with a second structure to be completed in 2006.

As research continues, Scripps Florida is creating a new hub of scientific exchange in the region. In March, the institute launched a series of high-level biomedical science seminars, named The Scripps Florida Collaborative Seminars, featuring prominent Florida-based speakers from the academic, biotechnology, and pharmaceutical communities. Their presentations focus on topics within the broad fields of biomedical science, advanced technologies, and drug discovery.

These Scripps Florida Collaborative Seminars create new opportunities to share knowledge, exchange viewpoints, and build collaborations among biomedical researchers at Scripps Florida and other Florida institutions.

Reaching out to an even broader audience, in November Scripps Research held the first Scripps/Oxford International Biotechnology Conference, hosted jointly with Oxford University at the Breakers in Palm Beach. The conference, “Building a New Model for Bioscience, Biotechnology, and Bio-medicine,” and pre-conference highlighting research in neurodegenerative diseases of aging and drug discovery technologies drew leading scientists and business executives from around the world.

The initiative built on the relationship between Scripps Research and Oxford University forged in 2003 with the announcement of the new Skaggs Oxford Scholarships Program, a joint graduate program in biology, chemistry, and biochemistry, in which students graduate with a Ph.D. jointly awarded by the two institutions.



The first Scripps/Oxford Biotechnology Conference drew scientists from Scripps California and around the world.



“Scripps Florida represents a new era for the institute—one that renews our commitment to forward-looking biomedical research, embraces promising technologies in drug discovery, and draws on resources from both coasts to strengthen and energize our institution.” RICHARD A. LERNER, M.D.

Science in the Community

In 2005, Scripps Florida also launched programs aimed at bringing science into the local community.

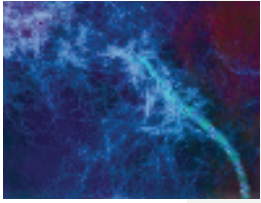
For the first time, labs at Scripps Florida hosted summer interns. Three teachers and four students, all from schools in the Palm Beach County School District, spent seven weeks learning hands-on techniques and participating in the life of a working lab. A two-year grant from the William R. Kenan, Jr. Charitable Trust supports these internships and additional outreach initiatives under development in Florida.

The Scripps Florida internship program is modeled on a similar program on the California campus, which also added new features this year, including a project to donate microscopes to San Diego schools.

INNOVATIVE INVESTIGATIONS

Scripps Research is known around the world for innovative research in a range of biomedical disciplines—work that changes the way we think about the workings of health and disease.

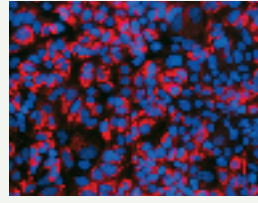
In 2005, Scripps Research scientists continued to make major contributions to their fields. In fact, at the time of this writing, Chemical Abstracts Service, a division of the American Chemical Society, has listed papers from Scripps Research investigators in its “Science Spotlight”—a list of the top-ten most requested articles worldwide—every quarter for the last year and a half. →



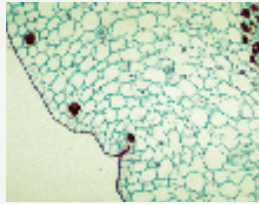
AMYLOID



SOY BEANS



HEPATITIS C



CROWN GALL DISEASE



Scripps Research studies contribute to the body of scientific knowledge that will make a difference in our lives.



HIV ANTIBODY

To highlight only a few of the breakthroughs of 2005, Scripps Research investigators:

- + Solved the structure of a rare human antibody that broadly neutralizes human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS).
- + Created the first cell culture system for hepatitis C virus, a new tool for vaccine and drug research.
- + Reported a new molecular mechanism that controls how the lungs are kept dry and under what conditions they permit fluids to enter, which may lead to new treatments for "shock lung."
- + Conducted one of the first studies looking at the long-term neurological effects of nicotine addiction on the brain's reward system, reporting findings that may have significant implications for people trying to quit smoking.
- + Revised our understanding of the process of RNA folding.
- + Showed that a certain type of molecule known as an LPA receptor plays a major role in conception.
- + Described how a bacterial control agent prevents crown gall disease, a plant disease that affects more than 600 species.
- + Discovered that a compound extracted from soy beans is a natural and potent inhibitor of a pathological process involved in a number of "amyloid" diseases.
- + Developed a way to screen hundreds and potentially thousands of "noncoding" RNA molecules to discover their functions within cells.
- + Pursued new approaches for combating antibiotic resistant bacteria.
- + Elucidated mechanisms and components of the immune system, including CD1, CD22, CD36, and TLR3.

Such studies contribute to the body of scientific knowledge that will make a difference in our lives.



New tools are available to focus on specific proteins that are essential for all organisms, many of which have implications for human health and disease.

NEW SUPPORT, NEW POSSIBILITIES

The pioneering investigations at Scripps Research received significant new support in 2005.

Major Grants

In the public realm, a consortium of scientists at Scripps Research and several other California institutions received \$52.7 million in funding from the National Institutes of Health (NIH). The grant is part of the second phase of a national effort called the Protein Structure Initiative that ultimately seeks to find the three-dimensional shapes of all types of proteins. This structural information will help reveal the roles that proteins play in health and disease.

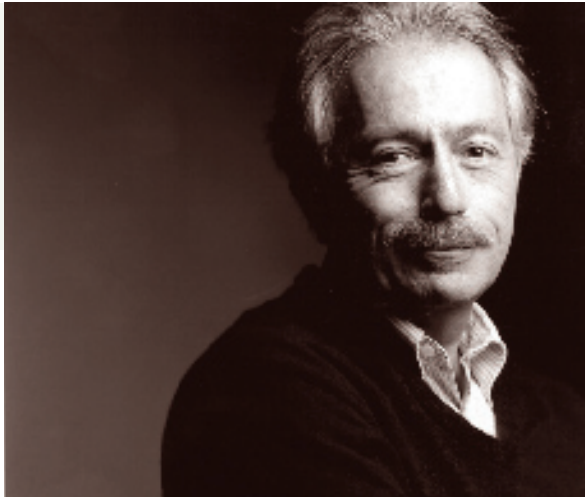
In addition, the NIH awarded a \$10.4 million grant to establish The Scripps Research Institute Molecular Screening Center, an initiative of researchers from both the California and Florida campuses. This pilot program aims to discover small molecule tools for translating basic biomedical discoveries more quickly into medically relevant applications. Significantly, this type of work, which has traditionally been done by pharmaceutical companies, is a first project of its kind in the public/non-profit sector.

Generous Gifts

Scripps Research also received many generous gifts from private donors, including two multi-million donations.

In the largest gift that has been made to Scripps Florida to date, Mr. and Mrs. Lawrence J. De George of Jupiter, Florida, gave \$5 million to support biomedical science at the institute's new Palm Beach County campus. The gift was made through the Lawrence J. and Florence A. De George Charitable Trust, established through the couple's leadership role in three Fortune 500 public companies.

On the West Coast, San Diego business leader and philanthropist John J. Moores contributed \$4 million to Scripps Research to establish the Worm Institute for Research and Medicine (WIRM), whose mission is to combat the painful, disfiguring, and debilitating diseases borne by worms that afflict hundreds of millions of people in much of the world. As one of its first efforts, WIRM will look for ways to detect the presence of parasitic worms in a person's body as a diagnostic tool for public health efforts in the field. →



Floyd E. Bloom



Tamas Bartfai



Steve Kay

PEOPLE NEWS

New Trustees Enrich Board

In 2005, several new members joined our Board of Trustees. I extend a warm welcome to J. Gary Burkhead, a retired Fidelity Investments executive, of Palm Beach, Florida; Louis L. Gonda, founder of International Lease Finance Corporation, of Beverly Hills, California; and Mark S. Skaggs, an attorney and business executive formerly with American Stores, of Boise, Iowa. All three new members will enrich the board with their expertise in business development and management, investment, and philanthropy.

Changing of the Guard

On the La Jolla campus, Floyd E. Bloom announced his retirement as chairman of the Scripps Research Department of Neuropharmacology, recently renamed the Molecular and Integrative Neurosciences Department. Floyd, now professor emeritus at Scripps Research and chairman and chief scientific officer of Neurome, was awarded an honorary degree at Scripps Research's 2005 commencement ceremony.

Taking up the chairmanship of the department is noted neuroscientist Tamas Bartfai, director of Scripps Research's Harold L. Dorris Neurological Research Center, who holds the Harold L. Dorris Chair in Neuroscience. Before arriving at Scripps Research in 2000, Tamas headed central nervous system research at Hoffman-La Roche.

Spanning both the California and Florida campuses, a new department, the Department of Biochemistry, made its debut in November. Headed by Steve A. Kay, Ph.D., who also directs the Institute for Childhood and Neglected Diseases, the department will take an integrative approach to research on physiological processes from the molecular level to the whole organism.

Also, 2005 saw changes in the administrative offices. Executive Vice President Arnold LaGuardia retired after serving the institute for more than two decades. Polly Murphy, senior vice president for business and scientific services, arrived from the Salk Institute for Biological Studies, and Robert Murphy (no relation), senior vice president and general counsel, joined Scripps Research from the business world, where he has worked for health care and technology companies.

Class of '05

Congratulations to the 21 newest alumni of Scripps Research's Kellogg School of Science and Technology, which *U.S. News and World Report* ranks among the top ten graduate programs in the nation in the biological sciences and chemistry. This year's Kellogg School graduates were awarded doctoral degrees in the May 20 commencement ceremony, which celebrated their individual accomplishments and contributions. 2005 graduates have gone on to hold positions in both academia and industry, including Albert Einstein University, Brown University, Providence Medical Center, Merck, Max Planck Institute, and Biogen.



Clare Waterman-Storer



Peter K. Vogt



Eng Tan



Gerald Joyce

Academic Accolades

Numerous awards and honors were bestowed upon the Scripps Research faculty in 2005:

- + Associate Professor Clare Waterman-Storer won the NIH Director's Pioneer Award, which supports exceptionally creative scientists who take innovative approaches to major challenges in biomedical research.
- + Professor Peter G. Schultz, who holds the Scripps Family Chair and is a professor in the Department of Chemistry and The Skaggs Institute for Chemical Biology, was awarded the American Chemical Society's Arthur C. Cope Award, which recognizes outstanding achievement in the field of organic chemistry, the significance of which has become apparent within the previous five years.
- + Professor Gerald Joyce was honored with the H.C. Urey Medal, the highest recognition by the International Society for the Study of the Origin of Life, given every six years to a single scientist who is considered to have the best sustained scientific research program in the origins-of-life field.
- + I received the DART/NYU Biotechnology Achievement Award from the Biotechnology Study Center of the New York University School of Medicine, which recognizes the role of leaders who pursue pure science in the development of pharmaceuticals, and particularly honor those scientists whose work has led to major advances at the bedside.
- + Professor John Yates was awarded the Distinguished Achievement Award in Proteomics, given in recognition of indispensable contributions to the field of proteomic science.

- + Professor Peter K. Vogt was elected as a fellow of the American Academy of Arts and Sciences, which selects fellows through a highly competitive process that recognizes individuals who have made preeminent contributions to their disciplines and to society at large.
- + Professor Eng Tan was the first non-European rheumatologist to be awarded the European League Against Rheumatism Meritorious Service Award, which recognized his work on autoantibodies and autoimmunity.
- + Professors Dennis Burton and Michael Buchmeier were elected to the fellowship in the American Academy of Microbiology, an honorific leadership group that recognizes excellence, originality, and creativity in all subspecialties of the microbiological sciences.
- + Professor Julius Rebek, Jr., was named a foreign member of the Academia Europaea, an organization of scholars from across Europe that is a "broad assembly of excellence."

Our Greatest Resource

At Scripps Research our greatest resource is our people. Our talented principal investigators. Our generous donors. Our hardworking staff. Our knowledgeable trustees. Our inquisitive students. Our outstanding postdocs. Our supportive friends. The accomplishments of Scripps Research are only possible because of your efforts.

Richard A. Lerner



Jerold Chun, M.D., Ph.D., is working to understand LPA signaling, which may shed light on certain types of childhood mental disorders, schizophrenia, and infertility.



*“Fat [molecules]
have new roles
that we are only
beginning to
understand.”*

JEROLD CHUN, M.D., PH.D.

Fat, Brains, and Pregnancy

JEROLD CHUN MAKES SOME SURPRISING CONNECTIONS

From a distance, the brain looks in many ways like every other organ in the body: it’s a tissue made up of a collection of various specialized cells that contribute to its particular functions. The brain is perhaps more diverse in its specialties than some of the body’s other organs, controlling everything from higher reasoning to autonomic activities, but it’s still fundamentally just another organ.

Up close, however, to the biologists who study the brain in detail, its complexity renders it distinct.

A single neuron in the cerebral cortex—the part of the brain that’s believed to be involved in higher functions like memory, cognition, and the interpretation of sensory input—might have synaptic connections with ten thousand other neurons. And when you consider the roughly 100 billion neurons in the brain, the interconnectivity of the neuronal cells becomes almost unfathomable. Even if we could enumerate and map them all, we still might not understand the brain any more than we would understand the entire infrastructure of New York by standing at the ramp of the Holland Tunnel counting cars.

One of the consequences of this cerebral complexity, says The Scripps Research Institute’s Professor Jerold Chun, M.D., Ph.D., is that scientists

do not understand the mechanisms of some of our most common drugs, like antipsychotics and antidepressants. “We do not understand,” says Chun, “how a lot of neuroscience drugs—given to millions of people—work.”

While many of the biggest breakthroughs in pharmacology—like morphine—were discovered prior to our knowledge of how they work, many people still suffer from neurological and neuropsychiatric diseases for which there are inadequate or suboptimal therapies. Several years of grappling with this problem led Chun to realize that he wanted to go back to the most basic question—how the brain works.

“If you do not understand how the brain works, how are you going to make medications for it rationally?” he asks. To Chun, the real secret to understanding the brain is not identifying the parts, but understanding how they are put together. For this reason, Chun has spent much of his career studying the developing brain, looking for molecules responsible for generating its diversity and complexity. His findings have implications for basic philosophical and psychological questions, such as what makes a person unique, to pressing medical and social ones, such as how to therapeutically address neurodegenerative diseases. →

“We would like to see this information become medically useful, and by understanding how these molecules affect various organ systems we can do that.” JEROLD CHUN, M.D., PH.D.

A SIMPLE MOLECULE FOR BRAIN DEVELOPMENT

Beginning in his days as an M.D.-Ph.D. student at Stanford University, working with neurobiologist Carla Shatz, Ph.D., and then later as a postdoc in the laboratory of Nobel laureate David Baltimore, Ph.D., at The Rockefeller University and the laboratory of Rudolf Jaenisch, M.D., at the Whitehead Institute, Chun has been interested in lipids—fat—a class of molecules that can be found in every cell and every tissue of the human body, although with cultural infamy.

“People understand and are aware of fat,” says Chun. But what people may not be aware of, he adds, is that some of that fat is really important for a spectrum of topics related to human health—and not in the way that one might expect. While dietary and bodily fat has certainly gotten much deserved attention for its connection to heart disease, diabetes, and other health-related issues, many types of fat are not as famous: lipid molecules that are essential for human health, including everything from fetal development to adult pregnancy.

Fat and pregnancy?

To understand this connection, one must travel back a few years to when Chun was on the faculty of the University of California, San Diego studying a fat molecule called lysophosphatidic acid (LPA), a phospholipid. Phospholipids, molecules of fat with a charged head on one end, are commonly found in biological organisms and are generally regarded as essential structural components of cells. For instance, bilayers of phospholipids are the primary component of cellular membranes, those essential barriers that define the boundaries of cells, keep-

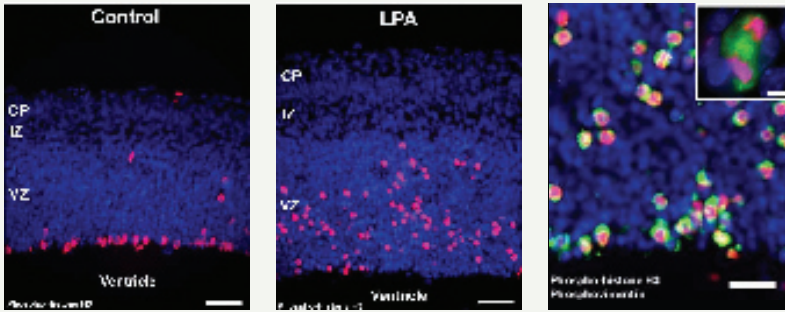
ing the molecules inside a cell separated from those outside a cell. LPA belongs to a family of phospholipids known as “lysophospholipids.” They are called “lyso-” phospholipids, says Chun, because years ago the early German chemists noticed that when red blood cells were exposed to the molecules, the cells would lyse open.

But Chun and his colleagues believed that LPA and many other phospholipids are more than just simple structural elements. They speculated that some of them play significant roles in the cell as signaling molecules. About ten years ago, they showed this was indeed the case when they identified the first cellular receptor to which LPA binds. When they knocked out the receptor, the signaling disappeared. Since then, eight more of these receptors have been identified.

“I think there will be a growing number of these receptors identified over the next few years,” says Chun.

Chun, who has a medical background, is drawn to this area of research because of its potential to improve human health. LPA receptors belong to a class of molecules known as G-protein coupled receptors (GPCRs), a common type of receptor molecule in the body, and an important class of targets for the design of drugs. Indeed, about half of the medicines on the market target such GPCRs.

“We would like to see this information become medically useful,” he says, “and by understanding how these molecules affect various organ systems we can do that.”



dia. 1

LPA in developing brains

When developing brains are exposed to LPA (lysophosphatidic acid), the number of cells increases. One mechanism for this increase involves neural stem cells (identified by the green label) that undergo increased cell cycle exit in response to LPA.

A COMPLEX FUNCTION

Chun and his colleagues have been pursuing basic research on LPA and its receptors to try to understand their roles, particularly in the brain. Within the nervous system, LPA receptors have a remarkable effect. Recently, in fact, Chun and his colleagues found that these receptors can act as signals that induce neurogenesis—the formation of new neurons. Previously, scientists believed that growth factors and other proteins largely controlled neural development and neurogenesis, but Chun and his colleagues discovered that when LPA binds to receptors in the embryonic brain, the result is a brain that shows a vastly increased number of neurons in the cerebral cortex.

Interestingly, LPA works not by causing neuronal progenitor cells in the brain to proliferate and then become neurons, as one might expect, but by a mechanism whereby the neuronal progenitor cells are prevented from dying and other neuronal progenitor cells are forced to divide prematurely.

Remarkably, LPA also induces folds in the brain. When developing brains are exposed to LPA, the brains spontaneously form gyrated structures that are characteristic of higher mammals, like humans. These gyrations increase the surface area of the cerebral cortex, the part of the brain believed to be essential to higher functions like intelligence and reasoning. Such gyrations are not normally seen in the brains of animals such as mice.

The work is significant because it may help clinicians and scientists understand some of the many diseases that arise from developmental defects that may be related to LPA signaling. The work may

shed new light on several childhood mental disorders and certain types of schizophrenia that are believed to be developmental in origin. Moreover, LPA receptors are molecularly similar to receptors for a related lipid called S1P, which has been implicated in multiple sclerosis, as well as immunological processes that Chun has been studying in collaboration with his Scripps Research colleague, Professor Hugh Rosen, M.D., Ph.D.

And Chun recently made the unexpected discovery that LPA receptors are critical in yet another area of biology—fertility and conception. In a paper published in a spring 2005 issue of the journal *Nature*, Chun, Senior Research Associate Xiaoqin Ye, and their colleagues at The University of Tokyo, Washington State University, and the Fred Hutchinson Cancer Research Center reported that mice that lack LPA receptors, which normally appear on the surface of cells in a mouse's womb, have fertility problems. These mice are able to produce eggs normally, but the resulting embryos, which are otherwise healthy, have problems implanting in the womb—the last step in conception.

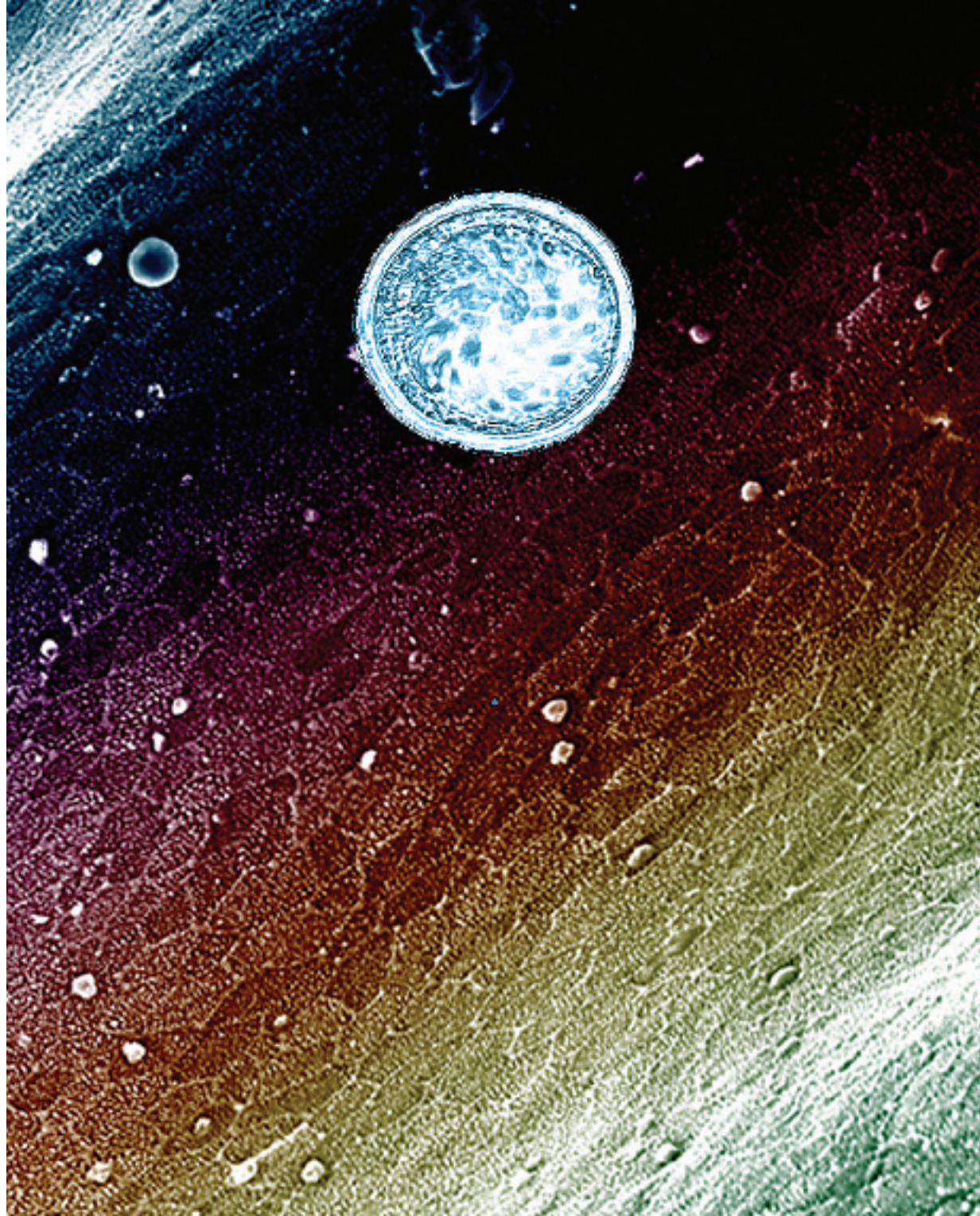
This work suggests that these proteins might make good targets for therapeutic intervention, perhaps even leading to new treatments and successful pregnancies for some of the more than 6 million American women affected by infertility.

INFERTILITY AND IMPLANTATION

In the Western world, the last few decades have seen a dramatic shift in when women are choosing

Strides in Understanding Fertility

The research of Jerold Chun, Ph.D., and colleagues has shown that LPA is a critical factor.



“Here is a clear effect on the ability of embryos to implant and position normally.”

JEROLD CHUN, M.D., PH.D.

to have their first children. According to the U.S. Centers for Disease Control and Prevention, the average age of first-time mothers increased from about 21.4 in 1970 to nearly 25 in 2000.

Many women wait until they are well into their thirties or later before having their first child. In fact, the CDC reports that in 2002, the latest year for which statistics are available, more than 100,000 women over the age of 40 gave birth. This was the first time that this number topped 100,000 in a given year. The success of these women at childbearing belies the difficulty that many women over the age of 30 have in getting pregnant. Infertility becomes more pronounced for mature women who are attempting pregnancy because a woman’s egg production decreases with age, especially after the age of 35.

Successful conception depends on a variety of factors. A man has to produce an adequate amount of healthy sperm, and a woman has to produce healthy eggs. The sperm has to be able to travel up the fallopian tubes to reach the egg, and once there, it must be able to fertilize the egg. Finally, the fertilized egg must become a viable embryo and implant in the uterus. Problems can occur in any one of these steps along the way and cause infertility. A man might not produce enough sperm, or his sperm might be unable to reach the eggs. A woman might have problems producing eggs or her fallopian tubes may be blocked.

Often, women will undergo treatments for infertility that range from taking hormones to stimulate ovulation to having their eggs harvested by doctors, fertilized by their partner’s sperm outside their bodies, and finally having the early embryos implanted directly into their wombs (the technique of *in vitro* fertilization).

Despite the existence of these therapies, however, the molecular mechanisms that govern female infertility are not completely understood. In fact, the cause of infertility is not always easy to diagnose. The American Society for Reproductive Medicine estimates that the cause of infertility remains a mystery in about 20 percent of all cases.

One issue may be that once a woman’s egg is fertilized and made into an embryo, it must descend to the womb and implant there, where it will grow into a fetus. But the factors that control whether an embryo is able to implant successfully inside a womb have not been known. One of these factors, according to Chun, is fat.

Chun and his colleagues created what is known as a knock-out mouse model for a specific LPA receptor. These are special mice that lack one or more particular genes of interest—in this case, a gene that encodes a particular LPA receptor called LPA3. With such a model, scientists can determine some of the overall physiological effects of an LPA receptor protein. In this case, analyses revealed that the spacing of the embryos in the womb was altered, and the number of implanted embryos was reduced (mice have litters of pups, typically giving birth to eight or so offspring with each pregnancy). Also, instead of the normal types of implantation, the embryos were clustered and many of them ended up sharing a placenta.

“Here is a clear effect on the ability of embryos to implant and position normally,” says Chun. “[It identifies] a new molecular influence—a small fat molecule—on this whole process.”

Chun, Ye, and their colleagues went on to show that losing LPA receptors affected prostaglandin levels. Prostaglandin is a fatty acid found in mammals that is essential for normal implantation. Manipulating parts of LPA signaling may thus be a way of changing prostaglandin levels.

This is a significant finding because low implantation rates are one of the major issues facing women who use assisted reproductive technologies, and nobody has ever considered LPA signaling to be involved in implantation. If the same pathway turns out to be relevant in human embryo implantation, then there might be a way to stimulate LPA signaling with a drug that would increase the odds of implantation for women undergoing assisted reproduction.

JASON SOCRATES BARDI



“What I’m trying to do is push the field forward—to open up the therapeutic possibilities in a broad sense.”

HUGH ROSEN, M.D., D. PHIL.

Breathing Easier

HUGH ROSEN'S WORK MAY HELP POTENTIAL VICTIMS OF "SHOCK LUNG"

Hugh Rosen, one of the newer faculty members at The Scripps Research Institute, is a man of many talents. He is a medical doctor, with a D.Phil. degree from the University of Oxford. He's an accomplished researcher, with postdoctoral work in immunology at Oxford and a decade with Merck Research Laboratories in Rahway, New Jersey as a senior research fellow, then executive director of immunology research. And now at Scripps Research, you could say he's a genealogist of sorts.

His most recent work, on pulmonary edema, is the result of years of study on the interrelationship of a family of signaling lipids that act on a family of receptors. (Lipids, an important part of living cells, are fats or oils that contain carbon, hydrogen, and oxygen.) The members of this receptor "family" of molecules have a sequence that overlaps or is identical at the gene level and at the protein level.

"What I've been working on is the shared genetic inheritance of this lipid receptor family," says Rosen, who was born and raised in Cape Town, South Africa, and whose English is measured and precise. "My lab has been working to define the roles of these lipids to better understand exactly how they regulate physiology and pathophysiology, and how they can cause things to go wrong."

Rosen's rigorous and strategic approach to understanding these molecules has been focused recently on the S1P₃ receptor, a protein expressed on the surface of the cell lining of the lung's air sacs. Earlier this year, his work paid off: it led to a breakthrough in understanding disease mechanisms in the lung, findings that were published in the journal *Proceedings of the National Academy of Sciences*. And this discovery holds great promise for people stricken with acute respiratory distress syndrome, also known simply as "shock lung."

WHAT IS SHOCK LUNG?

Shock lung can be caused by smoke inhalation, a severe blow to the chest, an extreme case of pneumonia, septic shock, severe blood loss, or drug overdose. Although the causes vary greatly, the situation for a patient who arrives at an emergency room with it is typically the same—critical. The syndrome leads to the filling of the lung's airways with fluids, a condition known as pulmonary edema. This further leads to a reduction of oxygen intake, which can rapidly degenerate into complete respiratory failure.

"It's a serious complication that often results in death," Rosen says. →



Hugh Rosen, M.D., D.Phil., and his colleagues are reporting a new molecular mechanism that controls how the lungs are kept dry and under what conditions they permit fluids to enter.

Shock lung is usually treated by ventilation that increases the oxygen available to the lungs, as well as by antibiotics, muscle relaxants, pain relievers, and heart stimulants. “The sole biologic reagent approved right now, as far as I know, is activated protein C,” says Rosen. “It deals with some of the intravascular coagulation that occurs as part of respiratory distress syndrome.”

According to the U.S. National Heart, Blood, and Lung Institute, these therapies have helped greatly. While in the past fewer than half of all people who developed this syndrome survived, now as many as seven out of ten receiving critical care in a hospital do.

Hoping to improve matters further, Rosen and his Scripps Research colleagues are reporting a new molecular mechanism that controls how the lungs are kept dry and under what conditions they permit fluids to enter. The mechanism involves activation of the S1P₃ receptor. When the receptor is activated, the lungs become leaky, leading to pulmonary edema.

“The receptor is activated by the presence of ligands, molecules that bind to specific receptors. In this case, it’s S1P₃’s natural ligand—sphingosine 1-phosphate,” Rosen explains.

And because the S1P₃ receptor is known to be involved in pulmonary edema, blocking this receptor may be a way to improve the prognosis for people with shock lung.

“We’ve postulated that it would be therapeutically useful to block this receptor. Our goal in the academic setting is to figure out the physiological rules. It will likely be in the pharmaceutical or biotech setting where the blocking of the receptor is actually accomplished.”

THE COMPLEX SIMPLICITY OF OUR LUNGS

Though the lungs are compact enough to fit inside our rib cages, lung tissue is a catacomb of airways and air sacs so elaborate that the air cavities inside the lungs encompass an area about 40 times larger than the surface area of the entire body.

If our lungs are healthy, taking a breath is an effortless action. We don’t usually give it a thought. But taking in oxygen and giving up carbon dioxide in exchange is actually a complicated physiological process.

Breathing is achieved through contracting the diaphragm to enlarge the chest, thereby reducing the external pressure on the lungs, allowing them to expand. This action creates suction, and we take in fresh air. Expelling oxygen-depleted air, rich in carbon dioxide, is achieved as the diaphragm returns to its resting place and the thoracic cavity is shortened, adding external pressure to the paired lungs and literally squeezing air out of them.

The respiratory system of the lungs proceeds, tree-like, with about 17 levels of branching between the trachea

and the bronchioles. The trachea, the main trunk of the system of tubes, splits into the two primary bronchi—dual passageways to each lung. From there, the air continues on its hyper-swift journey to the ends of the bronchi, which bifurcate like thousands of stems from a tree trunk into about 30,000 tiny bronchioles in each lung.

At the ends of the bronchioles, the indrawn oxygen streams toward its target: cherry-like clusters of air sacs known as alveoli. And though these individual air sacs are tiny, the total surface area of the alveoli is the size of a tennis court. It is in the alveoli that the indrawn breath reaches its target and comes to rest, the gas exchange with blood occurs, and carbon dioxide starts the return journey out of the body.

And the alveoli are where Rosen has focused his research into pulmonary edema.

WHY DO LUNGS FILL WITH FLUID?

A small lipid may be the trigger that causes acute respiratory distress syndrome, according to Rosen and his colleagues in their recent landmark publication. The culprit lipid is called sphingosine 1-phosphate (S1P), a member of the family Rosen has been investigating. S1P, it turns out, is produced at sites of inflammation. The activation of S1P₃ receptors in the lung by S1P may lead to pulmonary edema by causing a breakdown of the cellular covering that serves as a barrier preventing fluid from entering the lungs.

This work started as a collaboration between Rosen and his neighbor down the hall at Scripps Research, Jerold Chun, M.D., Ph.D. Both researchers had spent a number of years studying various lipids and lipid receptor systems in the body, including sphingosine 1-phosphate. This lipid is produced or secreted throughout the body, including in the lungs, where it has been found in the lung fluid taken from patients with asthma.

“We wanted to know what effect sphingosine 1-phosphate has on edema, so we looked at the effect of the lipid on the cells lining the lung and the blood vessels surrounding the lungs. In this work, we used mutant mice that Jerold’s group had created, mice lacking the S1P₃ receptor,” Rosen explains, adding that the work was supported by grants from the National Institute of Allergy and Infectious Disease, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke, as well as Kyorin Pharmaceutical Company.

Here’s what the researchers already knew. On the blood vessel side, the endothelial cells lining the capillaries express a type of protein known as S1P₁ receptors. Activation of these receptors by the sphingosine 1-phosphate leads to the tightening of junctions between the endothelial cells and, consequently, the stoppage of potential leakage—the

opposite of what happens in edema. However, the epithelial cells on the lung side express a slightly different type of S1P receptor called the S1P₃ receptor protein.

And here's where another Scripps Research investigator and Rosen lab member was able to fit an important piece into the S1P₃ puzzle. Yasuhiro Gon, M.D., Ph.D., had found that when sphingosine 1-phosphate is administered into the lung sacs of mice, it activates the S1P₃ receptors on the airway side of these epithelial cells and induces pulmonary edema. "Significantly, we found that a mouse with no receptors of this type is protected against pulmonary edema when exposed to sphingosine 1-phosphate," says Rosen.

Why does the sphingosine 1-phosphate induce lung leakage? To answer this, Rosen and Gon turned to their collaborators Malcolm Wood, Ph.D., and William Kiosses, Ph.D., in Scripps Research's Core Microscopy facility. They applied fluorescence microscopy to sections of tissue that had been exposed to sphingosine 1-phosphate and showed that the leakage occurs because the activation of S1P₃ receptor signaling causes disruptions in the integrity of the tight junctions between epithelial cells. Tight junctions are sealants that prevent the passage of molecules and ions through the space between cells.

Electron microscopy revealed that the tight junctions had been lost.

While Rosen is pleased to have made this discovery that may impact the future of pulmonary edema, he stresses that this finding is just one example of how the S1P system works. "We've shown the critical role of the S1P₃ receptor in its control of normal heart rate. We've shown the S1P₁ receptor is critically involved in control of the immune system, and now we've gone on to show that the S1P₃ system plays a role in pulmonary integrity and in the generation of pulmonary pathology. The challenge we've taken on is to understand the basic wiring of the system and learn how to manipulate it biologically and chemically to achieve good outcomes for patients. What I'm trying to do is push the

field forward—to open up the therapeutic possibilities in a broad sense."

THE SURPRISES AND PLEASURES OF RESEARCH

Asked how he thinks about this recent project these days, now that the results have been published to some acclaim, Rosen pauses for a few seconds, seemingly thrown off a bit by the question.

"Well, you know, science is funny. Sometimes you struggle with a problem and spend weeks—months—coming at it from different directions to solve it. Sometimes things go really easily, and in this project that's what happened. And I attribute that to the colleagues I worked with."

Rosen adds that one of the joys of research is mentoring bright up-and-coming colleagues, which was "a happy part" of this project. "I can't say enough about the contributions from my postdoctoral fellow and colleague Yasuhiro Gon. The training of colleagues is tremendously rewarding to me and is what has made this work particularly special." Gon, a graduate of the Nihon University School of Medicine in Tokyo, came to Scripps Research specifically to work on this project. "I believe Scripps has provided a springboard for his long-term career development when he returns to Japan," Rosen says, adding, emphatically, "It's been an absolute delight working with him."

Rosen says he wants to make one final comment about the pulmonary edema project. "The biggest surprise and biggest pleasure in this work was to see how the distribution of receptors and mechanisms are so neatly compartmentalized spatially to support tissue organization. It's strikingly aesthetic, and finding elegance in science is perhaps what pleases me the most about the work I do. There are those moments when the organization lays itself out in front of you, and you stand back and say, 'Wow!'"

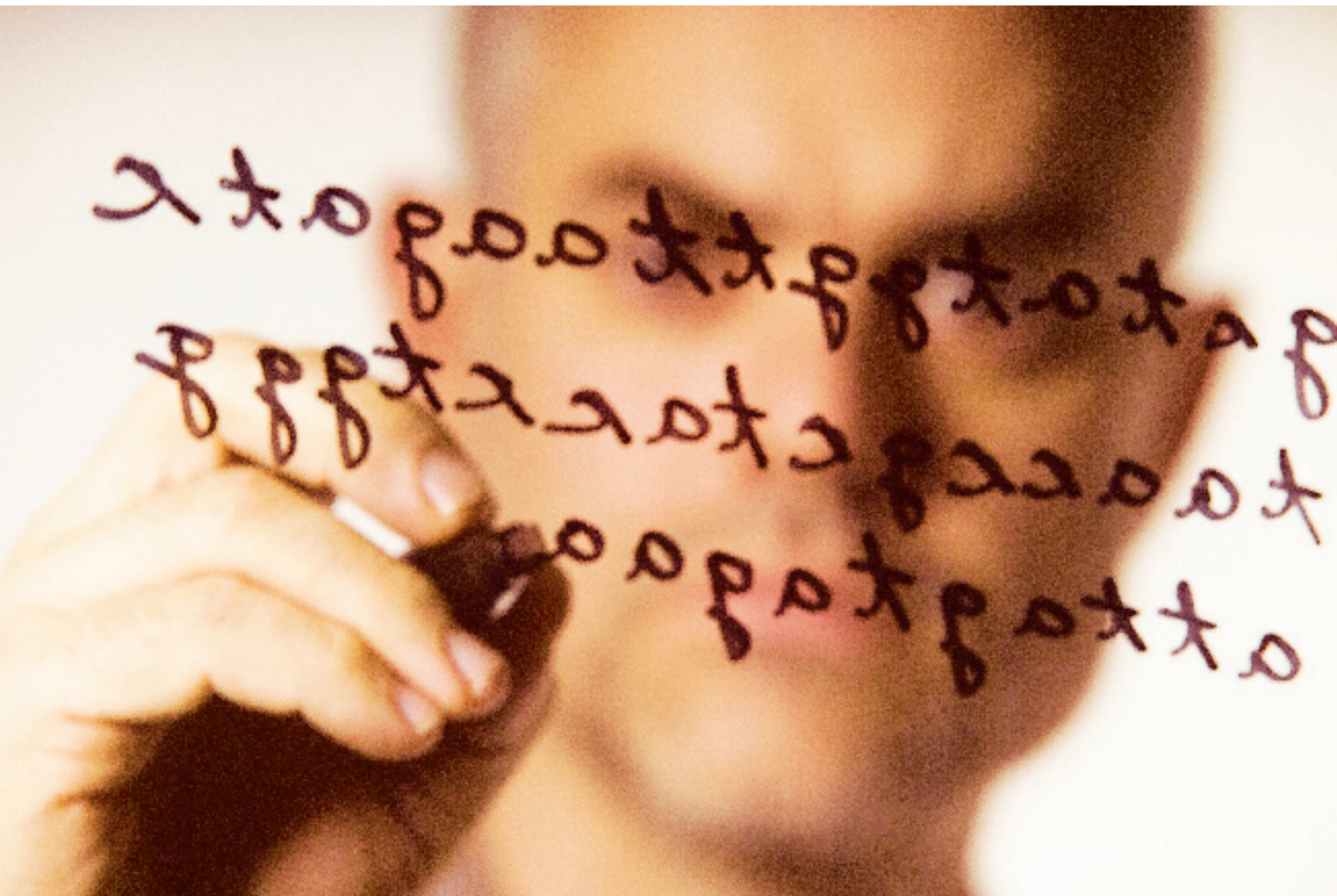
JEFF WORLEY

TOOLS TO SPEED MEDICINE

Hugh Rosen is a busy man. Among his projects is leading a group of researchers at the La Jolla, California, and Palm Beach County, Florida, campuses of Scripps Research to establish The Scripps Research Institute Molecular Screening Center, recently funded by a \$10.4 million dollar grant from the National Institutes of Health (NIH). This is a pilot program to discover small-molecule tools for translating basic biomedical discoveries more quickly into medically relevant applications.

The Scripps Research screening center, together with nine screening centers from the public and private sectors, will comprise the Molecular Libraries Screening Centers Network, a part of the NIH's strategic funding plan, the Roadmap Initiative. These centers will conduct high throughput screens against various biological targets to uncover "proof-of-concept" molecules useful in studying human health and in developing new treatments for human diseases.

Rosen notes, "Our goal is to provide tools for the broad scientific community so that we can accelerate the pace of the application of chemical biology to the understanding of physiology and pathophysiology."



FLOYD ROMESBERG AND HIS COLLEAGUES ARE STUDYING THE MECHANISMS INVOLVED WITH DNA REPLICATION AND CELL MUTATIONS THAT MAY HAVE IMPLICATIONS FOR TOPICS AS DIVERSE AS BACTERIAL DRUG RESISTANCE, CANCER, AND DISEASES OF AGING.



“I am proud that Scripps Research encourages people like me to step outside their field, to go in different directions.” FLOYD ROMESBERG, PH.D.



The Pragmatist

FLOYD ROMESBERG OFFERS A NEW TAKE ON EVOLUTION

It all began when Floyd Romesberg, Ph.D., decided to look at the fundamentals of DNA replication through the eyes of a chemist who understands the importance of biology. Last year, Romesberg, an assistant professor in The Scripps Research Institute Department of Chemistry, delineated the mechanisms of a key protein involved in mutations in bacteria—a discovery that may one day lead to effective therapy against bacterial drug resistance. Since then, Romesberg and his colleagues have expanded on those initial findings, opening the door to new studies that may uncover the same key proteins in humans and lead to a host of therapies for conditions from cancer to diseases of aging.

Romesberg's findings, published in the June 2005 issue of *PloS Biology* (the open-access, peer-reviewed publication *Public Library of Science*), describe how LexA, a protein in *Escherichia coli*, operates as an internal mutation engine. These mutations give the global pathogen the evolutionary advantage of resistance to common antibiotics, such as ciprofloxacin and rifampicin. What the Romesberg study showed was that the evolutionary drive—and the resulting drug resistance—could be stopped by blocking LexA.

CHEMICAL BIOLOGIST BY CHOICE

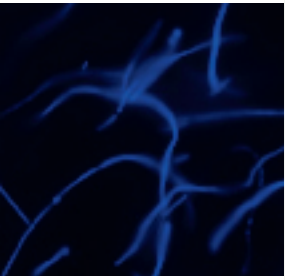
Romesberg, a chemist by training and a chemical biologist by choice, came to Scripps Research in 1998 after postdoctoral work at the University of California, Berkeley, where he trained with Peter Schultz, Ph.D., who is now a professor of chemistry and Scripps Family Chair of The Skaggs Institute for Chemical Biology at Scripps Research. Born in the Midwest, Romesberg did undergraduate work at Ohio State University and received his Ph.D. from Cornell.

“I was trained as a chemist, and I have reductionist thinking on my side,” he says. “Young chemists are often told to focus on chemistry first and the biology will come later. Biology isn't easier than chemistry; it's just different. But in biology you sometimes try to understand things without a lot of detailed explanations. As a chemist, I think *a lot* about details.”

DNA replication and the origin of mutations are important to the entire spectrum of human health—aging, drug resistance, cancer. Scientists have known for years that cells use polymerase enzymes to replicate DNA and that there is a chance,

“The more mutations you produce, the more you also increase the chances that they will kill you. That’s the brutal aspect of evolution.”

FLOYD ROMESBERG, PH.D.



Bacteria exposed to the antibiotic ciprofloxacin respond with cell protection mechanisms and increased mutations.

MUTATION ON DEMAND

however rare, that over the course of billions of base replications some mutations occur. That was pretty much that.

The problem that Romesberg observed was that every cell has extra polymerases—in bacteria there are actually five different replication polymerases. Since only two are needed to replicate DNA, he asked himself what the other three were doing there. To Romesberg, the extra polymerases suggested they were doing far more than merely replicating the genome.

Something else that Romesberg uncovered came from studies published more than a quarter of a century before. If scientists delete a specific gene (and its expressed protein) cells behave normally—except that they don’t mutate. In fact, you can’t make them mutate, no matter what you do to them. This phenomenon, Romesberg says, has been observed in cell types ranging from bacteria to mice to humans. Whatever that deleted protein was, Romesberg realized that it was needed to induce mutations.

In bacteria, one of these proteins turns out to be LexA, a repressor that cleaves its own amino acid chain to control the expression of about 30 different proteins involved in the repair of DNA damage, delay of cell cycle division, and mutation. Without LexA, there would be no mutations. And without mutations, there would be no recurring problems like the evolutionary resistance to antibiotics seen in potentially dangerous bacteria like *E. coli*.

Evolution has always possessed, at least in the popular mind, an image of overpowering force, like a kind of invisible *tsunami*. It washes over the natural world at random moments propelled by forces beyond our control, and in its wake leaves a multitude of mutational changes that carry the world up the evolutionary ladder.

But Romesberg’s research points to a different source of that power—the heart of the cell. Under duress, Romesberg’s research shows, cells can initiate their own mutations, producing evolutionary changes at a significantly faster rate than might normally occur. This ability to mutate on demand is an inherent response to stress—which occurs when a bacterial cell is being attacked by an antibiotic, for instance.

If the cell is threatened beyond its normal ability to self-repair, this built-in survival mechanism activates and the cell produces error-prone DNA polymerases whose sole task is to make mutations—in other words, to accelerate the process of evolution.

Using mouse models—one novel aspect of Romesberg’s research that makes it so compelling—he and his colleagues blocked the ability of LexA to control the expression of these polymerases, halting the bacteria’s ability to mutate. After being given antibiotics, the mouse models showed no signs of drug resistance over a three-day period. (In the control group with active LexA, researchers found that *E. coli* cells had developed high levels of antibiotic resistance during the same period).

Graduate student Tucker Roberts draws out mechanisms of replication fork repair in the face of DNA damage.



“It was there in the literature for 30 years,” Romesberg says, “but it got tied up in genetics and people began to argue about whether it was part of Darwinian or Lamarckian theory. They were very passionate in their arguments—and they’re still passionate today. This is where a chemist can bring a different perspective. A chemist can say, ‘Hmm, this debate raises some interesting questions, but if you could design drugs that prevent bacteria from mutating then you’d really have something.’ I’ve talked to several of the people who worked in this field for years and they were genuinely surprised by this approach.”

While antibiotics are one of the great success stories of the last century, in recent decades several antibiotic-resistant strains of bacteria have emerged, including those that cause TB, pneumonia, cholera, staph infections, and typhoid. Once thought to be almost eliminated, these strains are making a comeback, forcing physicians to treat patients with costly alternative antibiotics. Although new antibiotics are being created, our race against bacteria is neck and neck. A random walk through the factoid forest shows just how close it is.

According to the Centers for Disease Control:

- + Nearly 2 million patients in the United States acquire an infection in the hospital each year;
- + Of those, about 90,000 die each year as a result of their infection—up from 13,300 in 1992;

- + More than 70 percent of the bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly used to treat them;
- + Persons infected with drug-resistant organisms are more likely to have longer hospital stays and require treatment with second or third choice drugs that may be less effective, more toxic, and more expensive.

Expensive is an understatement. Treating multiple drug-resistant bacterial infections can be 100 times more expensive than treating normal infections. The World Health Organization estimates the total cost of treating all hospital-borne antibiotic-resistant bacterial infections at around \$10 billion a year.

Romesberg’s discovery may mark a critical tipping point in this ongoing battle.

Consistently pragmatic, Romesberg has started a new biotechnology company to help produce tangible benefits from this research and, he says, the biotechnology community has responded positively—unusual at a time when the conventional wisdom says that you can’t start a company based on a single biological concept.

THE DEAL WITH NATURE

There is another aspect of Romesberg’s discovery, one that is hinted at towards the end of his lab’s

“This is the deal we made with nature. In order to evolve, we have to risk screwing ourselves up. One mutation may bestow an advantage, another may lead to cancer. Aging, in fact, is just the irrevocable loss of information due to billions of small mutations.” FLOYD ROMESBERG, PH.D.

recently published article, “Inhibition of Mutation and Combating the Evolution of Antibiotic Resistance.”

“Everything in evolution is aimed at propagating DNA,” he says. “Because in the end the cell cares *only* about replicating its DNA. While the detailed mechanism that we wrote about in the *PloS Biology* paper has never been written down before, I don’t consider it to be unique to bacteria. It holds true across all cells, including human cells. It underlies all evolution.”

Humans don’t possess LexA like *E. coli* but we do have something just like it. Currently, Romesberg and five of his colleagues are searching for the human equivalent of LexA. They are first studying the problem in yeast. As it turns out, humans are pretty darn similar to yeast. Virtually all the proteins involved in DNA replication and cell cycling in humans were first identified in yeast. So far, the researchers have identified 15 genes in yeast and have eight human homologues. Those are being tested *in vitro*; the task after that will be to look at mouse models in human oncology, another place where mutation plays a critical role.

“This is the deal we made with nature,” Romesberg says. “In order to evolve, we have to risk screwing ourselves up. One mutation may bestow an advantage, another may lead to cancer. Aging, in fact, is just the irrevocable loss of information due to billions of small mutations.”

Here’s how Romesberg describes the effect of mutation on the human body: “Let’s say that on the day you’re born, you’re given a story book and you have to transcribe what you read in it every day. Over time you’re going to make errors in your transcription. You might make an error that makes the story better, that’s a beneficial mutation—a rare mutation. You also might make an error that kills off the main character—the equivalent of a cancer error. But the normal outcome would be spelling errors. At first, you will still understand the story in context, but in time the story will lose cohesion and eventually become incomprehensible. That’s aging.”

But for practical purposes, mutations are created the same, whether they’re selected or not and whether they are good or bad. It is the utter randomness of it all that is central.

“There are lots of theories about the randomness of mutations,” Romesberg says. “One of the tenets of the neo-Darwinist movement of the 1930s was that mutations happen at a constant rate. My work shows that evolution—mutation—rates are not constant and that during times of stress, your cells actively increase your chances of achieving a positive mutation. But the more mutations you produce, the more you also increase the chances that they will kill you. That’s the brutal aspect of evolution.”

With evolution so much in the news, it is no surprise that Romesberg’s name has started to crop up in what has become a growing national discussion, sometimes polite, sometimes not. Occasionally, he will type his name along with the word evolution into Google to find that his work is being cited by both sides of the debate.

Because while Romesberg’s discovery clarifies the process of evolution in one way, it muddies it in another. Have we, in fact, simply evolved to evolve? Is flux the ultimate order of things? And how efficient is a system that pushes evolution forward by depending on chance to succeed?

Ever the chemist, Romesberg remains determinedly, perhaps even stubbornly, a pragmatist above the fray.

“People will get passionately involved in these fights,” he says. “But the most important point is that these systems that are required to create mutations offer an opportunity to develop a vastly different therapeutic strategy—which is where we’re headed. When I think about making an impact with my work, I am proud that Scripps Research encourages people like me to step outside their field, to go in different directions. I’m a chemist who thinks seriously about biology, and part of a place that rewards this type of thinking.”

ERIC SAUTER



Focus on Education and Outreach

“Science today is so complex, detailed, interdisciplinary, and expensive that rarely can one researcher work effectively alone.”

RICHARD A. LERNER, M.D.

Kellogg School Joins M.D. – Ph.D. Program

Among the entering class of The Scripps Research Institute’s Kellogg School of Science and Technology this fall were candidates for an M.D.-Ph.D. program new to the institute, the Medical Scientist Training Program, involving both Scripps Research and the University of California, San Diego (UCSD).

“We’re excited to enter this collaboration with UCSD’s medical school,” says Jeff Kelly, Ph.D., dean of the Kellogg School and vice president for academic affairs. “The perspective of these academic physicians in training will enrich both our students and faculty.”

The Medical Scientist Training Program, funded by the National Institutes of Health, offers education in both clinical medicine and biomedical research. Students complete requirements for both medical school and a doctoral program in the sciences, and graduate with both M.D. and Ph.D. degrees.

Previously, UCSD medical students pursuing the joint M.D.-Ph.D. degrees had the option of working in research labs at UCSD, the Salk Institute, the Scripps Institute of Oceanography, or the Burnham Institute. Now, they may also choose from among labs at Scripps Research, whose graduate program is ranked by *U.S. News & World Report* as among the top 10 in chemistry and biology in the nation.

The M.D.-Ph.D. track at Scripps Research is supervised by Professor Gerald Joyce, himself a graduate of the Medical Scientist Training Program at UCSD and the Salk Institute. →

“Chemistry has become increasingly relevant for the development of new therapies”

LISA STOWERS, PH.D.,
Scripps Research Assistant Professor

“When I was at UCSD, I had to jump through hoops to pursue my interest in chemistry,” he says. “The collaboration with Scripps Research will offer Medical Scientist Training Program students more options, helping to attract world-class students to both institutions.”

Scripps Research Assistant Professor Lisa Stowers, Ph.D., who holds an adjunct position at UCSD, is another faculty member involved in the collaboration.

“As a member of the admissions committee for incoming UCSD medical students, I have been seeing highly qualified applicants specifically attracted to the UCSD medical school-Scripps Research combination,” she says. “This opportunity is exactly what they are looking for.”

Stowers observes that the alliance between Scripps Research and UCSD reflects not only the interests of individual students, but also changes in the fields of science and medicine. “Chemistry has become increasingly relevant for the development of new therapies,” she notes.

24

EDUCATION + OUTREACH

New Scripps Florida Seminars Encourage Collaboration

Scripps Florida has launched a series of high-level biomedical seminars—The Scripps Florida Collaborative Seminars—each featuring a prominent Florida-based speaker from the academic, biotechnology, or pharmaceutical communities.

“These seminars will serve as one of the major foundations for creating knowledge- and technology-sharing opportunities, team building, and collaborations among biomedical researchers at Scripps Florida and other Florida institutions and companies,” said Scripps Research President Richard A. Lerner, M.D.

The seminars, which began in March, focus on topics within the fields of biomedical science, advanced biomedical technologies, and drug discovery. Open to interested professionals within the Florida scientific community, the sessions are held on the Florida Atlantic University Jupiter campus, where Scripps Florida is currently operating.

“Collaborations among researchers are the lifeblood of contemporary biomedical science,” said Lerner. “Science today is so complex, detailed, interdisciplinary, and expensive that rarely can one researcher work effectively alone.”

Scripps Research scientists are involved in collaborations with researchers at other institutions worldwide, working as team leaders and members. These collaborations are usually initiated by the scientists themselves, who look to their network of colleagues when assembling a team for a particular research project.

With the recent development of its temporary campus in Palm Beach County, Florida, Scripps Research has also initiated collaborative arrangements on the institutional level. In one arena, Scripps Research and the University of Florida share magnetic resonance imaging technology. In another, Scripps Research joins forces with Florida State University on mass spectrometry instrumentation.

The Scripps Florida Collaborative Seminars will encourage further interaction among Florida scientists, providing opportunities for information-sharing and collaboration.

“As the Scripps Florida research staff gradually grows, its collaborations with Florida scientists will grow,” Lerner said. “The Scripps Florida Collaborative Seminars are one step in that process.”



Scripps Research scientists are involved in collaborations with researchers at other institutions worldwide.

“Keith Kellogg’s commitment to education was truly exceptional and we remain grateful for his extraordinary generosity and for his enthusiasm for the discoveries taking place at the institute.”

RICHARD A. LERNER, M.D.



Tribute to W. Keith Kellogg II

(1907 – 2005)

W. Keith Kellogg II, a well-known philanthropist who was a key supporter of The Scripps Research Institute, died on September 16 at the age of 98.

“We offer our deepest condolences to the Kellogg family,” says Scripps Research President Richard A. Lerner, M.D. “Keith Kellogg’s commitment to education was truly exceptional and we remain grateful for his extraordinary generosity and for his enthusiasm for the discoveries taking place at the institute.”

In 2002, Scripps Research named its graduate college “The Kellogg School of Science and Technology” in honor of Mr. Kellogg and his wife Janet (“Jean”) R. Kellogg, who were major donors to the program. In addition, the couple supported Scripps Research by endowing a chair in chemistry and making a significant contribution toward the Arnold and Mabel Beckman Center for Chemical Sciences. In recognition of their remarkable dedication, Scripps Research granted them honorary degrees in its May 17, 2002 commencement ceremony.

Born in Battle Creek, Michigan in June 1907, Keith Kellogg spent many of his formative years in a cereal factory, working for his grandfather, Will Keith Kellogg, inventor of the corn flake and founder of Kellogg Company, today the world’s leading cereal producer. At one point, Keith Kellogg headed the company’s packaging operation.

Later in his career, Keith Kellogg became chairman of General Packaging Products, a small, Chicago-based company founded by his father, John Kellogg, who pioneered the use of waxed paper in 1915. General Packaging prints protective packaging materials, like candy and frozen food wrappers. In the 1970s, Keith Kellogg retired and moved to California, where he lived in Rancho Santa Fe.

Over the years, Keith Kellogg became known as one of the country’s most devoted philanthropists, especially in the fields of science and education. He gave generously with his wife through their estate and through a foundation established in memory of his parents, Helen and John Kellogg.

The long list of institutions Keith Kellogg supported includes: the Kellogg Graduate School of Management at Northwestern University; the Kellogg Library at California State University, San Marcos; The John L. & Helen Kellogg University Art Gallery at Cal Poly Pomona (named after Mr. Kellogg’s parents), the Interlochen Center for the Arts in Interlochen, Michigan; the Boy Scouts; the Continuing Care Unit at Scripps Memorial Hospital-Encinitas; and the Kellogg Cancer Center in Evanston, Illinois.



Voices From Scripps Research Science Outreach Programs

To spread science literacy in the community and encourage high school students to consider a career in the biomedical sciences, Scripps Research now sponsors an array of science outreach—including summer internships for high school students and teachers in both La Jolla and Palm Beach County labs, spring seminars on contemporary issues in bioscience for San Diego teachers, a microscope donation drive in San Diego “Scopes in the Schools,” an enrichment program “Science Saturday” for Florida high school students, and a half-day “X-Sci” science festival on the La Jolla campus.

Are these efforts having an impact?

Here are some comments from people who should know:

Karena Haro, student at Castle Park High School, San Diego, who participated in the La Jolla summer internship program.

“Unbelievable! I’ve learned more these weeks at Scripps than I did for a whole semester in a science classroom. The environment, the experience... it is all great! I’ll never see science the same [way].”

Anand Parekh, student at Atlantic Community High School in Delray Beach, and 2005 Scripps Florida summer intern.

“I had a great experience working with Dr. [Nagi] Ayad, and feel that the Scripps internship has helped me develop a much greater respect and interest in biomedical research. The lessons I learned at Scripps are something that couldn’t be taught in a classroom.”

Sally Nguyen, teacher at Diegueno Middle School whose internship on the La Jolla campus was funded by Bank of America.

“Exposure to technology that [Scripps Research] scientists created and presently use has allowed me to create curriculum incorporating that same technology into my classroom. What an amazing opportunity my students will have this coming year!”

Fred Barch, science coordinator for the Palm Beach County School District, commenting on the new Scripps Florida summer internship program.

“We hope this is the beginning of a long relationship. The Scripps scientists have been extremely helpful in explaining the Scripps mission to our science teachers. The summer programs have generated enthusiasm and interest among our teachers and students who are excited about the possibility of working with some of the best scientists in the world. This interest in biotech will enhance our science program in Palm Beach County.”



Summer internships at Scripps Research expose high school students to biomedical science.

listen

learn

speak

Claire Luciano, student at San Diego High School, who participated in the La Jolla summer internship program.

“Before this internship I knew what gel electrophoresis does, but I had no idea how to physically load and run a gel and interpret the results. Working in a lab has helped me develop my goals; I will definitely be taking a second year of advanced biology in the upcoming school year.”

Richard M. Krasno, executive director and president of the William R. Kenan, Jr. Fund, which made a \$200,000, grant to support outreach activities at Scripps Florida.

“Although brand new, Scripps Florida brings more than 40 years of world-class research and reputation from its California campus to Florida, along with a world-class team of scientists who have come here from some of the best academic and commercial organizations anywhere.”

Scott Morone, biology teacher with Atlantic Community High School in Delray Beach, Florida, who spent last summer participating in an internship on the California campus and who sent a student to this year’s Scripps Florida internship program.

“I have a tremendous respect for Scripps. The people at Scripps exude an intelligence and competence that anyone would feel proud to be a part of. I think of [them] quite often.”

Ken Fish, Ph.D., former assistant professor on the Scripps Research La Jolla campus, who was the catalyst for the “Scopes in the Schools” program.

“The generosity of Olympus has allowed 12 San Diego junior high and high schools to incorporate the Olympus MIC-D digital microscope into their curriculum. This will surely help foster the next generation of scientists by allowing hundreds of local students for years to come to visualize the microscopic world around them.”

Zadig's Logic

EXCERPTS FROM THE 2005 COMMENCEMENT ADDRESS

BY FLOYD E. BLOOM, M.D.



Floyd Bloom, M.D.—distinguished neuroscientist, thoughtful mentor, and a leader in business and scientific publishing—delivered the keynote address for The Scripps Research Institute's 2005 commencement ceremony. Bloom is chairman, chief scientific officer, and founding CEO of Neurome, a La Jolla-based company, and Scripps Research professor emeritus. Here are excerpts from his remarks.

My experience with commencement addresses is limited to my prior address here for the 1996 class. Never having received an earned graduate degree myself, and not at all recalling whether we even had a commencement speaker for my medical graduation, I had little precedent on which to build.

After some pondering, I decided to focus my brief remarks today on three *facets* of the scientific life, some small residue of which may be useful to you as you move forth along your future career's development.

MARVELOUS POWERS OF OBSERVATION AND REASONING

Let me first remind you of an essential quality for the scientific life, known to some as Zadig's Method, or the insightful power of the curious observer. Zadig was a heroic character in a fable, who was endowed with marvelous powers of observation and reasoning. Voltaire, who wrote the fable in the mid-eighteenth century, modeled his description

of Zadig from an earlier sixteenth-century collection of stories about the travels of the three sons of the king of Serendippo, the book that had prompted the term "serendipity."

And serendipitously, I in fact found this entire description of Zadig by accident while reading a book of essays by the late English Social Psychiatrist Michael Sheppard while preparing myself to debate the enhanced value of Biological Psychiatry.

Zadig's method was well known and appreciated by T.H. Huxley, who termed it "retrospective prophecy," and concluded in an essay on the subject that: "The rigorous application of Zadig's logic to the results of accurate and long-continued observation has founded all those sciences which have been termed historical (archaeology, paleontology, astronomy, geology). This method is also the basis of what medical students are taught when they obtain histories of patient complaints in order to draw from these details the physical origins of their patients' problems.

Zadig's logic was also much appreciated by Professor Joseph Bell, a nineteenth-century Scottish surgeon who was said to possess the ability to diagnose people as they came through the door of his clinic. Bell was the professor and mentor of one Arthur Conan Doyle who later incorporated and somewhat exaggerated these analytico-synthetic skills into one Detective Sherlock Holmes whose classic powers of observation should be well known to you.

Zadig's logic will apply to every problem you encounter as you go forward into the world of experimental science—when you sense a question and ask yourself how did this come to be? It will be a skill that will serve you well when you ask, if it happens to emerge this way, if I pose this question in a new experiment, I should obtain this result.

... And it will apply especially when you do the properly framed experiment, with many of the right controls, and the results reveal themselves to be totally opposite of your prediction. It is then that you will need the keenest powers of

retrospective prophecy to move ahead because now surely you have an important problem worth pursuing.

THE ENDLESS FRONTIER

It may be clear from this tale that good teachers have enormous formative powers on receptive students, and you have no doubt experienced this in your training here. One of the many roles you will play will be to renew the graduate educational system that has shaped you thus far. For in science, as in much of life, knowledge of facts and a desire to discover new facts is not enough.

One also has a duty to the larger scientific community to help the system survive. Remember where the system of your education here arose—from the energies and support of your mentors and fellow students, and the lengthy lines of their predecessors in our system of graduate education.

The essence of this view was well expressed by one of my favorite intellectual icons shaping the American world of science after World War II, namely Vannevar Bush. Vannevar Bush almost single-handedly led the conversion of the academic scientific community from its contributions to the war effort into a peacetime in which Science was to be the endless frontier for the good of the public. Among other achievements, he also accurately predicted computerized information handling, hypertext, and desktop computers....

Even occasional observers of the scientific scene know that this past decade has witnessed some incredible achievements by the worldwide research community. In fact, the incredibility itself is the noteworthy feature—things once thought to be impossible have in fact been accomplished. Like the four-minute mile, which was once believed to be the limit of human running capacity, preconceived limits in several scientific fields have made obsolete. The continuous emergence of such advances suggests that other barriers that are acceptable by today's logic could eventually yield to persistent research.

Not only do we have high resolution inventories of human, mouse and rat genomes, we have the beginnings of haplotype clusters that may someday provide every newborn child with the known adult diseases to which that individual may be vulnerable without life long preventive maneuvers. Work with embryonic, adult, and umbilical cord stem cells may mature into the often-admired opportunities of regenerative medicine. New ways to study in experimental animals the pathways defined by genes that tip the balance towards pathophysiology in complex genetic disorders may lead to new targets and new synthetic chemical interventions to delay if not prevent these diseases in humans. I envy your future.

A CALL TO ACTION

Graduates of 2005, as you go forth to seek your fields of exploration, remember well those who have guided your way thus far, and renew your commitment to the long-term survival of the scientific edifice of knowledge. In my 2003 Presidential Address to the American Association for the Advancement of Science, I called attention to a dark cloud on our still endless horizons of sciences, the precarious nature of our healthcare system. Until solved, this long neglected problem presents a gigantic obstacle to the application of the discoveries flowing from biomedical research into de-

liverable standards of medical practice that could benefit all of society, both in the United States and globally.

Unless steps are taken toward a comprehensive restoration of our system, the profound advances in biomedical research so rapidly accruing today may never be effectively transformed into meaningful advances in health care for society.

There are signs that the federal government may finally take some actions to prevent the numerous errors committed in a system that is no longer able to cope with the pressures of daily practice by investing in modern methods of digital records exchangeable across time and distance and at least rise to the level of performance of today's ATM cards. Yet, intrusions into the traditional physician-patient relationship by increasing regulatory compliance requirements and third-party payers deciding issues of clinical practice are not simply onerous, they have soured the joys of practice and further reduced the time available for doctors to spend with their patients and to teach the next generations of physicians.

Scientists must now unite to insist that the system be prepared for the discoveries of the future and that we fulfill as quickly as possible the major needs arising from today's global health problems. We urgently need to begin the expansion and training of a new cadre of academicians to fill the gap between basic scientific discoveries that inform us about the unknown elements of the life process, and the practical steps needed to provide societal benefit from those insights. It is a form of science termed by the historians Holton and Bonnert as "Jeffersonian Science"—a form of use-inspired engineering of the kind that delivered transistors and lasers from the insights provided by physics, and novel products from modern chemistry.

May you have the satisfaction of many discoveries of your own before the time comes when it is your turn to address a graduating class. My very best wishes for your success.

Scripps Research Financial Highlights

FISCAL YEARS ENDING SEPTEMBER 30

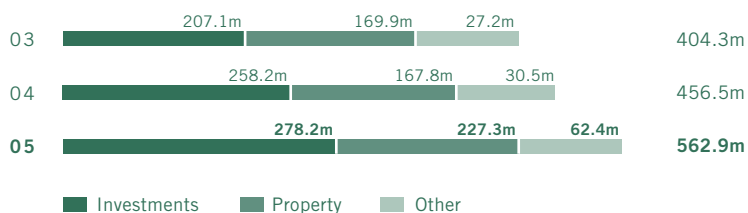
Sponsored Programs

(millions)

03		242.4m
04		265.3m
05		312.6m

Total Assets

(millions)



Net Assets

(millions)

03		316.6m
04		356.3m
05		420.9m

Asset/Debt Ratio

(millions)

03		(404.3/38.1) 10.6m
04		(456.5/36.8) 12.4m
05		(567.9/57.4) 9.9m

Net Income

(millions)

03		25.2m
04		39.6m
05		64.6m



Alice D. Sullivan
Chair, Board of Trustees

Letter from the Board of Trustees Chair

31

Dear Friends:

Private support for The Scripps Research Institute expanded significantly in the past year, through major gifts from new donors in California and Florida, leadership gifts from trustees on both coasts, and exciting new organizations and events designed to better recognize our donors while educating them about the progress of our science.

Since October 1, 2004, in California, Bill and Sharon Bauce pledged \$1 million to support our graduate program, and Trustee John J. Moores and his wife Rebecca gave \$4 million to create the Worm Institute for Research and Medicine (WIRM), a new center for research to combat river blindness and other diseases afflicting Third World peoples. Including a major gift received from the Skaggs family as part of the family's continuing commitment to Scripps Research, California gifts and pledges since October 1, 2004, exceeded \$15 million. →

Scripps Research received pledges and gifts of \$1 million from Floridians Marjorie Fink of Palm Beach, George and Wilma Elmore of Gulf Stream, Elizabeth Fago of Palm Beach Gardens, and Trustee Alexander Dreyfoos and his wife, Renate, of West Palm Beach. At our September 12 board meeting in La Jolla, another Florida trustee who, with his wife, prefers for now to remain anonymous, allowed us to announce their \$1 million gift, earmarked for Scripps Florida. Two weeks later, at a 300-guest luncheon to celebrate groundbreaking for our new Palm Beach County campus, Florida Governor Jeb Bush announced that Lawrence J. and Florence A. De George, residents of Jupiter, Florida, had pledged \$5 million to Scripps Florida, bringing private gifts and pledges from Florida since January 1, 2004, to \$12 million.

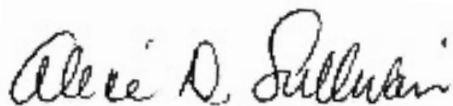
To better acknowledge and involve donors who might not also be trustees, in January the institute launched a new major-gift society, called The Scripps Council of 100, composed of individuals, couples, and foundation or corporate representatives who give at least \$100,000 a year or \$1 million or more over a lifetime to support Scripps Research. The group is advised by Katja Van Herle, M.D., M.S.P.H., the institute's director of community health education, and will meet once a year in California and once a year in Florida.

At the same time, individuals and families who have planned for Scripps Research in their wills were recognized by creation of The Scripps Legacy Society. These deferred-gift donors enjoyed their first event in April, a dinner held in Rancho Santa Fe, California. They are advised by Cheryl H. Dean, Esq., Scripps Research's planned giving counsel.

Finally, 1000 Friends of Science—an organization for annual donors of \$1,000 or more—was inaugurated in September at a dinner on our La Jolla campus hosted by President Richard A. Lerner, who spoke eloquently about the institute's extraordinary history, culture, and future. Following Dr. Lerner's remarks, six of seven California department chairs described the breakthrough work—and needs—of their scientists, creating a compelling case for increased private support. It was my last-minute assignment to substitute for our chemistry chair, who could not attend. As a lawyer, I must confess that I've never felt less prepared for a case.

As your trustee chair, I am more confident than ever that the case for giving to Scripps Research has never had greater appeal—anywhere, anytime, or to any audience.

Sincerely,



Alice D. Sullivan
Chair, Board of Trustees

Development Report

MAJOR DONORS TO THE SCRIPPS RESEARCH INSTITUTE

The Scripps Research Institute would like to thank its generous donors. Your support has helped fulfill the institute's mission to serve humanity by creating basic knowledge in the biosciences, by applying breakthroughs in research to the advancement of medicine, and by educating and training young scientists for biomedical research and its application to human welfare. 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 the commitment of contributors who have opened their hearts and supported Scripps Research this year. We give special recognition in sidebars to a few of the people and organizations whose gifts demonstrate how private philanthropy advances the work of Scripps Research scientists and the institute's educational and community outreach programs.

Asterisks (*) indicate trustees. Daggers (†) indicate deceased. Italics indicate faculty and staff.

33

SPECIAL ACKNOWLEDGEMENT FOR LIFETIME GIFTS

The following are individuals and organizations who over the years have pledged or given \$1 million or more to The Scripps Research Institute. They deserve special recognition for their lifetime dedication to the advancement of biomedical science.

Anonymous (8)	Ellison Medical Foundation	Mr.* and Mrs. John Jay Moores
Mr. and Mrs. L.S. Skaggs/ The ALSAM Foundation/ The Skaggs Institute for Research	George T. and Wilma Elmore	National Multiple Sclerosis Society Office Depot
American Cancer Society	Elizabeth Fago	Mark E. Pearson
American Heart Association	Marjorie Fink	Pitman Moore, Inc.
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Arthritis Foundation	Jim and Sue Gilstrap	Mr. and Mrs. Donald Roon
William and Sharon Bauce Family Foundation	Dr. and Mrs. Cecil H. Green	Mr. and Mrs. Leo Roon
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Arnold and Mabel Beckman Foundation	Virginia Hale	Mr. and Mrs. John Safer
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Cancer Research Institute	Lita Annenberg Hazen	Margaret Scripps Buzzelli
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Helen L. Dorris Foundation	Gladys Q. Knapp	Sam and Rose Stein Charitable Trust
Alexander W.* and Renate Dreyfoos	<i>Dr. Richard A.* and Dr. Nicola Lerner</i>	Buddy Taub Foundation
	Leukemia and Lymphoma Society	Dr. Andrew J.* and Mrs. Erna Viterbi
	Lucille P. Markey Charitable Trust	
	G. Harold and Leila Y. Mathers Foundation	

THE SCRIPPS LEGACY SOCIETY

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

Anonymous (17)	Mr.† and Mrs. John E. Goode, Jr.	Donna Prendergast
Eileen M. and John R. Anderson, IV	Mr. and Mrs. John L. Hanes	Mrs. Donald Roon
Mike and Stella Banich	Gloria and Gene Harper	<i>Dr. and Mrs. William R. Roush</i>
Bruce G. Barnes	Margaret E. Hastings	Martin I. Samuel
Mrs. William McCormick Blair, Jr.*	Mrs. Julie Hill	Dr. James H. Sands
Mrs. Joseph Brock	Alan R. Hunter	Estelle Schiller
David and Maggie Brown	Mr. Okey B. Johnson, Jr.	Mrs. Lesly Starr Shelton
Mrs. Michael Buckley	Virginia Kahse	William and Barbara Short
David S. and Pamela M. Carton	Mr.† and Mrs.* W. Keith Kellogg, II	Guy Showley
Stanley Corbin	<i>Jeffery W. Kelly</i>	Selma and Irving Singer
Gordon Corwin	Robert and Mary† Kerney	Mr. and Mrs. L.S. Skaggs
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Foundation	Mr. and Mrs. Sheldon Magazine	Mrs. Elizabeth Lowell Sutton
Helen L. Dorris Foundation	Walter and Eleanor Malen	Nina S. Tate
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James W. Farschon	Winona B. Mathews	Robert G. and Gloria R.† Wallace
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Allan R. Gilbert	Ms. Lillian Owens	Ms. Yvonne Wylie
Stanley H. Gist	Barton and Lorraine Palmer	John and Shirley Zeien
Eugenia C. Glow	Robert G. and Janette Park	

THE SCRIPPS COUNCIL OF 100

\$100,000 and above

American Cancer Society	Susan G. Komen Breast Cancer	Dr. Andrew J.* and Mrs. Erna Viterbi
American Heart Association	Foundation	Dr. John C. Whelton/Arthritis Foundation
William M. and Sharon Bauce	Leukemia and Lymphoma Society	Yvonne Wylie
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Foundation	Jr. Charitable Trust	
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Alexander W.* and Renate Dreyfoos	G. Harold and Leila Y. Mathers Charitable	
Richard J.* and Helen Elkus	Foundation	
George T. and Wilma Elmore	John Jay* and Rebecca Moores	
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Elizabeth Fago	Douglass Nosworthy	
Marjorie Fink	Mark E. Pearson	
Friedreichs Ataxia Research Alliance	Piziali Family Foundation/Community	
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Wayne R. Green	Damon Runyon Cancer Research	
Virginia Hale	Foundation	
Juvenile Diabetes Research Foundation	Mark S. Skaggs*	
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Research
National Hemophilia Foundation
National Multiple Sclerosis Society
Pediatric Dengue Vaccine Initiative
Robert P. Scripps
Wellcome Trust

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Helen Hay Whitney Foundation

35

DEVELOPMENT REPORT

FOR THE LOVE OF SCIENCE

Trustee *Alexander W. Dreyfoos* was born to the double world of art and science. The son of a photographer father and musician mother, he pursued a path involving synergy and serendipity by studying electronics, optics, and physics at MIT, earning an M.B.A. from Harvard, and inventing the Video Color Negative Analyzer (VCNA), a specialized closed-circuit color TV system used for determining the proper exposure of a color negative, and its later version, the Professional Video Analyzing Computer (PVAC). The motion picture version of the VCNA led, in 1971, to an Academy Award for technical achievement to Alex's West Palm Beach-based company Photo Electronics Corp.

Shortly after Governor Jeb Bush and Dr. Richard A. Lerner announced Scripps Research's expansion into Florida, Alex accepted the invitation to become the institute's first new Florida trustee. A lifetime appointee to the MIT Corporation and founding chairman of the Raymond F. Kravis Center for the Performing Arts, the inventor-entrepreneur brings vision, persistence, and a belief in the cross-pollination of ideas—along with devotion to detail—to every project, most recently MIT's dramatic new Dreyfoos Building, designed by Frank Gehry. A member of the American Academy of Arts and Sciences, he will be honored in January 2006 with the Woodrow Wilson Award for Corporate Citizenship by the Woodrow Wilson International Center for Scholars in ceremonies to be held at the Kravis Center in West Palm Beach.

In November 2004, he and his wife, *Renate*, announced a \$1 million gift to Scripps Research—"for the love of science"—at a dinner hosted for the institute's trustees there.

ALEXANDER W. AND
RENATE DREYFOOS



FOUNDERS' CIRCLE*\$5,000 and above*

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Dr. and Mrs. John Curnutte	Marriot Palm Beach Gardens	Robert K. Wechsler
Docutek Imaging Systems	Jennie McRoy	<i>Dr. Charles Weissmann</i>
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Robert J. Eichenberg	John Whitney Payson	Western Capital Mortgage

1,000 FRIENDS OF SCIENCE*\$1,000 and above*

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/ **FOR THE LOVE OF COMMUNITY**

Like legend but true, *George and Wilma Elmore*—newlyweds who moved to Boca Raton, Florida, shortly after George's discharge from the U.S. Army—opened their paving business in 1953 out of a single truck, borrowing \$500 to buy the road-roller that now rests in the lobby of Hardrives, Inc., their multi-million-dollar road construction company. At that moment, it may have seemed to Wilma, who came from California, that Boca Raton—created in the 1920s by another Californian, Addison Mizner—was as sleepy and slow as pre-Scripps La Jolla, another coastal resort town built around a brand name. Since then, both communities have become tourism and technology centers blessed with exclusive shops, expensive real estate, and worldwide brand recognition for quality and style.

The Elmore's business prospered with Palm Beach County, providing road surface for interstate highways, school and college campuses, and residential communities from Boca Raton to Jupiter. But the Elmore's never changed their character, or their values: hard work, honesty, and a profound love of people and place. By 7:30 a.m. most weekdays, George can be found at the office or in his car, checking on a construction job or driving to a board meeting for one of a dozen nonprofit organizations sprinkled around a county nearly as dispersed as San Diego. On weekends—and increasingly for Wilma, in the summer—the couple enjoys time at their second home in the mountains of North Carolina.

Their son *Craig* works at Hardrives. Their daughter *Debra*, who has returned to South Florida from a successful corporate career in Southern California, owns an IT consulting business and follows in her parents' footsteps, bringing financial sense as a volunteer to nonprofits in need.

When Scripps Research followed the same path east that brought Addison Mizner and the Elmore's to Florida, George and Wilma gave \$1 million—an essential endorsement in Palm Beach County—for the love of community.

GEORGE AND
WILMA ELMORE

\$1,000 and above (cont.)

Evelyn Friedland	Mr. and Mrs. G. Russell Ladd	Mr. and Mrs. James L. Ramsay
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Norman Guite
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Marian Guthrie
Mr. and Mrs. Donald E. Guy
Mr. and Mrs. Raymond L. Haight III

FOR THE LOVE OF HUMANITY

Lawrence J. and Florence A. De George of Jupiter, Florida, are among the most generous and respected members of South Florida's philanthropic community. Before moving to Florida, both followed successful careers in New York. Florence was a commercial interior designer and investor; George, a World War II veteran and graduate of Princeton and MIT, who earned a Ph.D. in applied mathematics from Columbia University before beginning a lucrative mergers-and-acquisitions career that culminated in the chairmanship of Amphenol Corp. (NYSE).

Now active as a merchant banker and lender, Larry serves as senior partner of DeG Capital Partners, and with Florence, as co-founder of the Lawrence J. and Florence A. De George Charitable Trust, supporting organizations such as Boys & Girls Clubs and the Juvenile Diabetes Research Foundation. Their son *Lawrence F. De George*, a graduate of the School of Veterinary Medicine at the University of Pennsylvania, is a successful business entrepreneur and Scripps Research trustee.

For the love of humanity through the advancement of bioscience, Lawrence J. and Florence A. De George's pledge of \$5 million to help build Scripps Florida was planned for maximum impact to coincide with Scripps Florida's September 23 groundbreaking, where it was announced by Governor Jeb Bush. Larry believes that, like philanthropy, political involvement is an important part of civic duty. He also gives this advice: "Good philanthropists don't invest without doing their due diligence and their homework."

LAWRENCE AND FLORENCE DE GEORGE

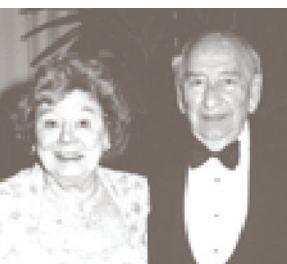


Photo by Davidoff Studios, Inc.

\$100 and above (cont.)

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Dr. and Mrs. Harold R. Hall
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Laverne Havran
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Mr. and Mrs. J. Michael McCulley
Mina McCutcheon
John T. McFarland
Mary L. McGhee
Stuart D. McIntosh
Margaret F. McIrvin
Mr. Keith C. McKeown

FOR THE LOVE OF TECHNOLOGY

Trustee *Andrew J. Viterbi* and his wife, *Erna*, are committed to finding advanced cancer treatments and bringing them quickly to patients. That is why they have made a generous \$2 million gift for cancer translational research at Scripps Research. With these funds, clinicians and researchers are working together on pre-clinical and clinical trials to determine whether a promising new compound is effective against a specific cancer, shepherding new treatments from the laboratory bench to the patient's bedside.

Andrew immigrated to the United States with his parents in 1939 as a refugee from Italy. He is co-founder of QUALCOMM, Inc., a leading developer and manufacturer of mobile satellite communications and digital wireless telephony, and is the inventor of the Viterbi algorithm, used for decoding convolutionally encoded data such as the error-correcting codes in cellular phones. Dr. Viterbi has written numerous research papers and three books, making substantial contributions to communications theory and its industrial applications. He received his Ph.D. in digital communication from the University of Southern California. In 2004, the university's engineering school was renamed the Viterbi School of Engineering in his honor.

A trustee of Scripps Research, he is a Life Fellow of the Institute of Electrical and Electronic Engineers and a fellow of the American Academy of Arts and Sciences. Among other honors, he was inducted into the National Academy of Engineering in 1978 and the National Academy of Sciences in 1996.

ANDREW AND ERNA VITERBI



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Mr. and Mrs. Ronald K. Mulcahey
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Milena Pesic
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Jolene Roth
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Virginia A. Schulz
Andrew Schwab
Connie M. Sciacca
Mr. and Mrs. Gerald A. Scott

FOR THE LOVE OF EDUCATION

William and Sharon Bauce have funded seven Kellogg School of Science and Technology graduate students in each of the past six years at The Scripps Research Institute. This year, they have committed to funding many more through a \$1 million contribution. The Bauces are experienced philanthropists, supporting numerous charitable causes in California and Oregon, including the Helen Woodward Animal Center, the YMCA of San Diego County, and the Rancho Santa Fe Community Center. Bill worked for many years as a manager and consultant in the cable television and cellular communications industries before retiring with Sharon to Rancho Santa Fe in the early 1990s.

The couple's continuous support of the graduate program helps ensure excellence in education and innovation at Scripps Research, where their vision and impact will be felt for generations to come.

BAUCE FELLOWS:

ANDREA MANUELL,
CHRISTINE FANG, AND
JASON JENS.



\$100 and above (cont.)

Carl W. Sedler
Mr. and Mrs. Raymond J. Settimo
Marcia A. Shaeffer
Shelly Jay Shafron
Jeanette Shammass
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Nina Blake Sharp
Daniel T. Shelley
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Leona Lee Sohn
Mr. and Mrs. Lyle Songer
Mr. and Mrs. Robert T. Sopko
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Genevieve Hull Watts
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Eugenia L. Weissman
Patricia R. Welsh
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Mr. and Mrs. John A. Wills
Enrique Wong
Kam Shing Mon Wong
Mr. and Mrs. R. Keith Woodstra
Lawrence O. Wright
Mr. and Mrs. Lewis L. Wright, Jr.
Harry S. Wurtz
Mr. and Mrs. Charles Yanofsky
Dr. David and Dr. Natalie Yates
Mr. and Mrs. John T. Zeien
Mr. and Mrs. Marvin Zepede

We have done our best to make this list an accurate reflection of gifts to Scripps Research from October 1, 2004 to September 30, 2005. If errors or omissions exist, please accept our apologies and call us at (858) 784-2037.

Thank you, Scripps Research Development Staff.

FOR THE LOVE OF INNOVATION

The Ellison Medical Foundation has funded projects at Scripps Research for a number of years. Recently, the foundation awarded the institute over \$1 million to support biomedical research and to develop creative and new research programs on aging. Thanks to the grant, Scripps Research scientists will conduct research on new targets for therapeutic intervention to develop new approaches for controlling age-related disease. In addition to aging, the foundation has established a program on global infectious diseases, an important focus of research at Scripps Research that is also funded by others, including Trustee John J. Moores and his wife, Rebecca.

The Ellison Medical Foundation is supported by Lawrence J. Ellison, CEO of Oracle, Inc., the world's leading supplier of software for information management and the world's second largest independent software company. A legendary innovator, Mr. Ellison is inspirational for what can be done with ambition, talent, and intelligence. He even thinks of altruism as a strategy of happiness: "Giving is the right and moral thing to do."

LAWRENCE J. ELLISON,
CEO of Oracle, Inc.



Opportunities for Giving

Gifts to The Scripps Research Institute fund cutting-edge research on prevention, diagnosis, and treatments for human disease by providing the margin of excellence and innovation that has distinguished the institute since its beginning.

EVERY GIFT IS IMPORTANT. Gifts made without restriction support laboratory work while helping provide the physical and human infrastructure required to support it. Gifts may also be designated for specific purposes, such as research on a particular disease, graduate school fellowships, or specialized equipment and technology. Gifts of real estate, gifts by bequest, and gifts using other planned giving vehicles, such as trusts, can offer attractive tax advantages and can be customized to fit the donor's needs

For more details, or to discuss your gift, please contact the development office in California at (858) 784-9367 or (800) 788-4931. Outside California, please contact the office of external affairs at (561) 656-6400. Or simply go to the Give Now page at www.scripps.edu/philanthropy

Here is more information on some of the current opportunities for giving.

UNRESTRICTED GIVING

In addition to laboratory research—the heart of the institute's work—unrestricted gifts help meet the costs of buildings and personnel which in other institutions, such as public universities, are subsidized by taxpayers. At Scripps Research, every unrestricted dollar supports research by insuring that scientists have well-maintained buildings, well-operated equipment, and well-qualified personnel available to them.

DISEASE RESEARCH PROGRAMS

Gifts can be designated for centers, programs, or departments:

THE CENTER FOR INTEGRATIVE MOLECULAR BIOSCIENCES

The Center for Integrative Molecular Biosciences (CIMBio) is a new collaborative effort to foster multidisciplinary studies of molecular machinery, with the aim of determining molecular structure, mechanisms of action, and dynamic behavior in the context of living cells and whole organisms. Current work at CIMBio focuses on developing critical new electron and light microscopy technologies for imaging molecular machinery at both structural and cellular levels.

THE HAROLD L. DORRIS NEUROLOGICAL RESEARCH INSTITUTE

The Harold L. Dorris Neurological Research Institute was founded in 1999 as the result of a long-term commitment by the Harold L. Dorris Foundation under the leadership of Helen L. Dorris.

The center investigates a variety of neurological disorders, including *schizophrenia* and *Alzheimer's disease*, as well as increasing scientists' understanding of the aging process in the brain. The center has attracted an international team of brain specialists, led

by Tamas Bartfai, Ph.D., former head of central nervous system research at Hoffman-LaRoche (a pharmaceutical company in Basel, Switzerland) and former chairman of the department of neurochemistry and neurotoxicity at Sweden's Stockholm University.

Naming Opportunities

The center seeks private funding to supplement the original grant of \$10 million in order to recruit additional senior faculty (named faculty chairs at \$1,500,000 each), establish named fellowships (\$1,500,000 each), and create visiting professorship appointments of four months (\$50,000 each). Specific program funding in the range of \$50,000 to \$300,000 for new scholars is also a priority.

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

The Helen L. Dorris Child and Adolescent Neuro-Psychiatric Disorder Institute was also established with a generous gift from Helen Dorris, a mental health advocate.

The institute was created to investigate the pathological basis of neurological and psychiatric disorders. Benjamin Cravatt, Ph.D., its director, leads in recruiting an interdisciplinary team of scientists to focus on understanding neuropathology in children and adolescents and finding new treatments for their conditions.

Giving opportunities

Gifts of all sizes are welcome. Contributions of \$1,000 or more entitle a donor to annual membership in The Scripps Research Institute's donor group, 1,000 Friends of Science. A commitment of \$150,000 will establish a research fellowship to support the work of a senior scientist for two years. A commitment of \$75,000 will help fund a laboratory bearing the name of the donor or loved one.

THE INSTITUTE FOR CHILDHOOD AND NEGLECTED DISEASES

For a number of years, researchers have attempted to use gene therapy and other treatments against *cystic fibrosis*, *muscular dystrophy*, *childhood deafness*, and certain forms of *cancer*. Although none of these efforts has led to consistent success, collectively they have laid the groundwork for more successful approaches. In other cases, such as *autism*, scientists are only now uncovering genetic clues that may lead to better treatments.

The majority of the world's population lives in developing countries where parasitic diseases such as malaria and river blindness remain pandemic. The institute uses the latest advances in biology to target therapies for these persistent problems.

Naming Opportunities

Gifts of all sizes are welcome; some naming opportunities are still available. A commitment of \$150,000 will establish a research fellowship to support the work of a senior scientist for two years. A commitment of \$75,000 will help fund a laboratory bearing the name of the donor or loved one.

THE PEARSON CENTER FOR ALCOHOLISM AND ADDICTION RESEARCH

Established in 2003 through a gift from Mark A. Pearson, a real estate investor-developer in Palo Alto, California, the Pearson Center combines the latest biomedical research with new clinical treatments to fight the devastating, costly, and deadly disease of alcohol and drug addiction.

The Pearson Center complements and reinforces traditional treatments by focusing on the physiological changes in the brain that drive excessive drinking and drug use and create vulnerability to relapse. Researchers are studying the ability of new compounds, designed at Scripps Research and elsewhere, to modulate the neurological effects of alcohol, reduce excessive intake, and prevent relapse by normalizing the brain during an alcoholic or addict's recovery.

The prospects for enhancing traditional treatment of alcoholism, addiction, and relapse through pharmaceuticals have never been more promising. At Scripps Research, scientists have identified a large part of the neuro-circuitry involved in the reinforcing action of alcohol, showing how this circuitry changes when a person progresses from social drinking to alcohol abuse and dependence and establishing working laboratory models that mimic this transition for use in preclinical and clinical drug studies.

ENDOWMENT

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

the life of the donor and will be both enjoyed and acknowledged by generations to come.

Naming Opportunities

A named faculty chair to be occupied by a dean, director, or department chair can be established by a gift of \$3,000,000; a senior faculty chair can be established for \$2,000,000. Other endowment opportunities—such as the High School Student and Teacher Science Training Program, which can be endowed with gifts of \$100,000 or more—are tailored to the donor's interests within the programmatic priorities of the institute.

SCHOLARSHIPS AND FELLOWSHIPS

THE KELLOGG SCHOOL OF SCIENCE AND TECHNOLOGY

Financial aid opens doors and makes dreams possible. Scholarships and fellowships support the best future scientists for Ph.D. study at the Kellogg School of Science and Technology, the graduate school of The Scripps Research Institute.

In 1989, Scripps Research established a Ph.D. program in macromolecular and cellular structure and chemistry. A second Ph.D. program, in chemistry, was created three years later to focus on synthetic and bio-organic chemistry. Both programs provide an exceptional opportunity for a select group of outstanding and intellectually diverse students. *U.S. News & World Report* has ranked Scripps Research's macromolecular and cellular structure and chemistry program ninth in the nation in biological sciences, and the chemistry program sixth in chemistry and second in organic chemistry.

Graduate and postdoctoral fellowships attract the very best applicants for graduate study—young men and women who will influence science, and society itself, as future leaders in education, research, and industry. Their ability to study at Scripps Research, regardless of family income, is critically important for the institute, for the nation, and for the future of world science.

Gifts of all sizes are welcome. A gift of \$25,000 will name and support a graduate stipend for one year; a gift of \$500,000 will endow a graduate student stipend in perpetuity. A gift of \$10,000,000 will permanently endow the graduate program.

INTERNSHIPS

HIGH SCHOOL STUDENT RESEARCH EDUCATION PROGRAM

Scripps Research's High School Student Research Education Program exposes students to basic biomedical research, provides hands-on laboratory experience, and motivates young people—particularly those students whose groups are historically under-represented—to continue their education in the sciences at this impressionable age.

Students participate in spring enrichment tutorials in molecular biology and chemistry, a summer research internship program

in a research laboratory, and a mentoring program with a Kellogg School graduate student who guides them through SAT test preparation, college selection, the application essay, and financial aid search.

SUMMER RESEARCH INTERNSHIP PROGRAM FOR TEACHERS

Study after study has found that American schools fall short in helping students achieve scientific literacy. A critical element in improving science education is effective teacher training.

Scripps Research's Middle/High School Science Teacher Summer Research Program exposes teachers to new laboratory techniques and procedures, informs them about contemporary issues in biomedical research, and forges long-lasting ties between secondary school educators and Scripps Research scientists.

The program emphasizes the scientific process, research planning, bench experience, experimental design, data analysis, and interaction with laboratory personnel. In addition to an intensive, hands-on, eight-week summer experience, teachers are expected to use the laboratory experience as a springboard to create and enhance their curriculum and to become resources for other educators.

UNDERGRADUATE SUMMER RESEARCH INTERNSHIP PROGRAM

Scripps Research's Undergraduate Summer Research Internship Program is an intensive eight-week research experience for talented undergraduate students currently studying biology, chemistry, mathematics, physics, computer science, cognitive science, or neuroscience.

The program exposes students to basic biomedical research, provides hands-on laboratory experience, and encourages them to continue their education in the sciences. The program is also committed to increasing the number of students drawn from communities historically underrepresented in the sciences.

Giving Opportunities

A gift of \$2,500 will support the participation of one high school or undergraduate student in the summer internship program.

A gift of \$5,000 will support the participation of one teacher in the teacher training program or fund a one-day teacher training seminar on contemporary issues in bioscience.

A gift of \$100,000 or more will endow an internship position for a student or teacher. Such a gift perpetuates the donor's philanthropy by creating a permanently funded program, named by or for the donor.

BUILDINGS AND LABORATORIES

Investment in critically needed buildings and laboratories helps ensure that The Scripps Research Institute can embrace the future with confidence. The equipment Scripps Research scientists need to do their work is as varied and sophisticated as

the work itself.

In Florida, a gift of \$5 million will name one of three new buildings under construction on land provided by Palm Beach County. In California, a gift of \$8 million will name the immunology building.

BUILDINGS AND LABORATORIES

Gifts can be made to fund the purchase of much-needed equipment or, in California, to support the renovation of existing facilities.

Scripps Research enjoys one of the world's leading private computational capabilities, with an array of computers. Research is also 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 advancing technology. New laboratory equipment is continually being developed to improve the efficiency and effectiveness of basic research, and new technology provides ever-shorter paths from discoveries to their application in prediction, diagnosis, and treatment of disease. Gifts of discretionary funding are critically important to support the ongoing modernization of laboratories.

IMMUNOLOGY DEPARTMENT

In 1961, internationally acclaimed immunologist Frank J. Dixon, Jr., M.D., came to the Scripps Clinic and Research Foundation—along with a team of young scientists that included Charles G. Cochrane, M.D., who retired as professor of immunology in 2005—to establish a department of experimental pathology—the genesis of The Scripps Research Institute.

Today, Scripps Research scientists focus on potential solutions for some of the world's most puzzling and pernicious diseases: lupus, diabetes, arthritis, prion disease, HIV, Ebola virus, bacterial meningitis, chronic inflammatory disease, cancer, and many others.

Using bonds, Scripps Research recently purchased its immunology building, designed specifically for the institute's core department and located near both of the institute's other signature buildings—the Beckman Building and the Skaggs Building. A naming gift of \$8 million will assure the donor an unparalleled opportunity for legacy.

Other Naming Opportunities

Other naming opportunities in the immunology building include the following:

Laboratory Floor	/ \$1,000,000
Large Conference Room	/ \$200,000
Individual Laboratory	/ \$75,000

Naming opportunities in Florida include the following:

Public Auditorium	/ \$3,000,000
Public Atrium	/ \$1,000,000
Public Lobby	/ \$1,000,000
Laboratory Floor	/ \$1,000,000
Large Conference Room	/ \$ 500,000
Small Conference Room	/ \$ 250,000
Individual Laboratory	/ \$ 200,000

Ways to Give

GIFTS OF CASH, CHECKS, OR CREDIT CARDS

An outright gift of cash is often the simplest way to give. It is not subject to gift or estate taxes, and the gift amount can be deducted from your federal income tax return. If the gift exceeds your gift ceiling for the year in which it is made, you may also be able to carry over the remaining deduction in succeeding years. This means that with careful planning, nearly every outright gift to Scripps Research can be deducted. To make a credit card gift, you can give at www.scripps.edu/philanthropy using our secure server, or call (858) 784-9367 in California—or (561) 656-6400 outside California—to provide your credit card information over the phone.

To make your gift with a check, please make it payable to The Scripps Research Institute, send it with a letter or note stating whether it is unrestricted or restricted to a particular purpose, and mail it to::

Development Office
The Scripps Research Institute
10550 North Torrey Pines Road, TPC2
La Jolla, California 92037
Phone: (858) 784-9367

GIFTS OF STOCK

Giving appreciated stocks or bonds may be more favorable than a cash donation. You can deduct the full fair market value of long-term appreciated securities and avoid tax on the capital gains, and you can deduct gifts of securities up to 30 percent of your adjusted gross income with a five-year carry-over option. Under certain circumstances, you can also qualify for a 50 percent annual deduction by reducing the value of your gift.

To answer questions about non-cash gifts of stock, bonds, or property, call (858) 784-2037.

NAMING GIFTS

The Scripps Research Institute provides many opportunities to name buildings, laboratories and public spaces; graduate and faculty fellowships; and internships for talented students and teachers.

To discuss these opportunities, in California please call the

major gifts office at (858) 784-9365. Outside California, please call the office of external affairs at (561) 656-6401.

GIFTS IN MEMORY OR CELEBRATION

You can make a tribute gift in memory of a friend or family member, in honor of someone special to you, or to recognize a person or couple on an anniversary, birthday, or other special occasion.

You can make your gift by phone, by mail, or at www.scripps.edu/philanthropy. We will send an acknowledgment card recognizing your gift to the person or persons you designate. The amount of your gift will not be revealed, but you will receive an acknowledgment letter noting the gift amount.

For more information on how to make a tribute gift or to make a gift by phone, please call (858) 784-2037.

CORPORATE GIFTS

Gifts from businesses and corporations continue to pay dividends by fostering the spirit of independence, innovation, and entrepreneurship that has characterized Scripps Research since its founding. Companies and their executives become involved in the institution's work as donors, as event sponsors, and at special recognition events. 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), complete it, then mail it to:

Development Office
The Scripps Research Institute
10550 North Torrey Pines Road, TPC2
La Jolla, California 92037

Many companies also find that association with scientific, educational, or public events presented by The Scripps Research Institute provides a ready-made way to reach intelligent, motivated customers, reward clients and employees, and create community good will.

Through professional conferences such as the Scripps/Oxford International Biotechnology Conference, public series such as *Frontiers in Science*—held quarterly in both California and Florida—and private events for donors, prospects, and community leaders, Scripps Research offers a menu of corporate branding opportunities on both coasts.

To discuss ways in which your company can enjoy the dividends of being a donor or a sponsor, please call (561) 656-6400.

FOUNDATION GIFTS

From the beginning, foundation support has helped make The Scripps Research Institute a world leader in science.

Almost every kind of foundation—public, independent, disease-focused, family-run—is represented on the institute's foundation wall of honor.

For more information about foundation giving, please contact the foundation office at (858) 784-8274.

ALUMNI GIFTS

Gifts from alumni of the institute's Kellogg School of Science and Technology are especially appropriate. Through its graduate school, the institution has invested in the future. From it, Scripps Research alumni have gone on to positions of eminence in their field, reinforcing the top-ten national ranking in biology and chemistry given The Scripps Research Institute by *U.S. News & World Report*.

Gifts from alumni send a clear message of support, gratitude, and respect, and they can be directed to the department that has had the greatest impact on the donor. They can also be made to help provide graduate fellowships, including those named to honor the donor or a faculty member chosen by the donor.

BEQUESTS

A bequest is a gift by will or revocable living trust. This is an excellent choice if you want to support The Scripps Research Institute in the future, but wish to maintain liquidity and use of your assets during your lifetime. A bequest is flexible; you can adjust the terms of your gift after it is established. The full amount of your gift is deductible from your taxable estate.

The three most common bequests are specific, general, and residuary. In a *specific bequest*, you name a particular item such as a piece of real estate or a block of securities that you wish to give. In a *general bequest*, you name the dollar amount you want to give. In a *residuary bequest*, you give a percentage of your estate after all specific and general bequests have been met. All bequests are fulfilled only after debts, taxes, and estate expenses have been paid.

A bequest can be *unrestricted*, enabling Scripps Research to direct your funds where future need is greatest, or *restricted* for a particular program or purpose at the institute.

For more information on bequests, please call (858) 784-2380.

GIFTS THAT PAY INCOME FOR LIFE

Charitable Gift Annuity

A charitable gift annuity is a contract between you and The Scripps Research Institute. You irrevocably transfer an asset to the institute—often cash, stocks, or other securities—and the institute agrees to make fixed annual payments to you for life. These payments are regulated by the California Department of Insurance.

Payments are a set percentage of the value of your asset, and the guaranteed rate you are paid is determined by your age when the gift is made. The older you are when you make the gift, the higher your percentage and your payment. If you choose payments to benefit two people, the rate is lowered, reflecting the payout for a longer span of time. The remaining value of your asset at your death or the death of your loved one is the resulting gift to Scripps Research.

The advantages to you are many. You can take an immediate charitable contribution deduction for a portion of the gift's value, and part of each annual payment may be tax-free. You may also be able to lower your estate taxes. If your asset is property that has appreciated, you may be able to avoid capital gains taxes.

Charitable Remainder Trust

Through this plan, you establish an irrevocable trust with cash, securities, or other property, then determine the terms of the trust: who the beneficiaries are, the percentage of the trust's value that will be paid out annually, how long the payments will be made, and which charity or charities receive the remainder.

A trustee (you, your financial professional, or someone else you choose) manages the assets; the income beneficiaries can be you or others close to you. The percentage paid to you must be at least five percent of the trust's value. Your income is either a fixed dollar amount or a set percentage of the value of the trust, depending on which plan you choose. You can also decide if you want the payout to be a set period of years or for the designated persons' lifetimes. When all of the payments have been met, or upon the death of the last beneficiary, the trust is dissolved and the remainder of the assets are paid to the charity or charities you have designated.

For more information on gifts that pay income for life, please call (858) 784-2380.

REAL ESTATE

A gift of a residence or vacation home is one of the most flexible in terms of benefits to you. Depending on how you structure your gift, you can minimize or eliminate taxes, earn additional income, and continue to live in your home.

Real estate is not limited to personal residences. It includes investment or commercial properties, agricultural properties, parcels of land, and more. All offer varying advantages, depending on whether you own the property outright or share ownership, and how much the property has appreciated. You can choose to give 100 percent or a percentage of the property to the Institute. You also can choose to donate any tangible personal property inside the building as a separate gift.

In most circumstances, your charitable contribution is based on the appraised value of the real estate at the time the gift is transferred to the Institute. Your deduction can equal up to 30 percent of your adjusted gross income. On an appreciated property, you avoid capital gains tax by donating the real estate to Scripps Research prior to its sale.

Real estate is quite versatile as a gift. You can use it as an outright gift or a bequest, or you can use it to fund a charitable remainder trust, a charitable gift annuity, or a lead trust. You also can retain a life estate with your donation.

Scripps Research's planned giving counsel at (858) 784-2380 can assist you in evaluating your property's potential and analyzing the options to determine the most beneficial course for you.

LIFE INSURANCE

You can make a substantial gift by naming The Scripps Research Institute a beneficiary or owner of your life insurance policy. Often, this plan enables you to make a larger gift to the institute than you otherwise could.

If you have an existing life insurance policy that is no longer needed to protect your children, your spouse, or your business interest, you can name the institute as the policy's beneficiary. Because the beneficiary designation is a revocable gift, you are not entitled to an income tax deduction; the value of the policy is deductible from your taxable estate. If you also transfer ownership of the policy to the institute, you can immediately deduct the current value of the policy from your income taxes; if you are still paying premiums, you can deduct the cost of those premiums each year.

You also can purchase a new life insurance policy to benefit the institute. With Scripps Research designated as the owner and beneficiary, you are entitled to an income tax deduction for your initial contribution and the premium payments each year. For more information on life insurance, please call (858) 784-2380.

GIFTS OF RESIDENCE WITH LIFE ESTATE RETAINED

When you donate your personal residence to Scripps Research, you earn an immediate tax deduction, and you can retain the right to live in and use your property for the rest of your life. You also may be eligible to earn supplemental income.

Life Estate Agreement

You can make a substantial gift of your home to The Scripps Research Institute without changing your day-to-day life at all. When you irrevocably transfer the title of your personal residence or farm to the institute, you can maintain exclusive use of the property for life.

Although this property does need to be a personal residence that you use, it doesn't need to be your primary residence. It can be a vacation home or second home. As long as you have use of the property, you are responsible for maintenance, upkeep, insurance, and property taxes, and you are entitled to any income it produces.

Your immediate tax deduction equals the value of the remainder interest, which the IRS code calculates as the present value of the Institute's right to use your property in the future. With this gift, you bypass the capital gains tax and you lower your estate taxes. When the property transfers to the Institute, it is used as you directed.

Life Estate Agreement with Gift Annuity

When you pair a life estate agreement with a gift annuity, you enjoy all the benefits of a life estate—a charitable deduction, possible capital and estate tax savings, and retained exclusive use of your property—and you receive a fixed annual payment for life.

Your payment is determined by two factors: the value of the remainder interest and your annuity rate established by your age

at the time of your gift.

For life estate plans, it is wise to consult with your attorney regarding the laws of your state.

For more information on gifts of residence with life estate retained, please call (858) 784-2380.

CHARITABLE LEAD TRUST

Through this giving plan, you establish a trust that provides annual income to Scripps Research for a set period, after which the remaining trust assets are returned to you or your heirs. This plan can substantially lower your gift and estate taxes.

Charitable Lead Trust Plans

A charitable lead trust is the reverse of a charitable remainder trust. Rather than benefiting at the end of a trust's term, as with a charitable remainder trust, the institute benefits at the beginning of a trust's term.

To establish a charitable lead trust, you transfer assets such as cash, securities, real estate, or other property into an irrevocable trust. The trust provides annual income to the institute for a set term, then returns the assets to you or your heirs. The benefits—which include income tax deductions and reduced or eliminated gift and estate taxes—vary, based on the terms you establish for your trust and whether the trust is enacted during your lifetime or as part of your will.

For more information on charitable lead trusts, please call (858) 784-2380.

Recognizing Our Donors

The Scripps Research Institute believes in informing, involving, and serving its donors. The institute's excellent reputation for stewardship of gifts, both large and small, has been well earned.

Scripps Research has three giving societies, each designed to inform, involve, and serve:

THE SCRIPPS COUNCIL OF 100

Members of The Scripps Council of 100 support the institute's mission by contributing \$100,000 annually or by making a single contribution of \$1 million or more. Gifts may be restricted or unrestricted.

Members are invited to meet each year in Palm Springs, California, and in Palm Beach, Florida, where they enjoy private sessions specifically designed for them with Scripps Research scientists who inform and update them on issues, trends, and discoveries in biomedical research, and with Katja Van Herle, M.D., M.S.P.H., professor of medicine and director of community health education, who helps translate that research into terms of patient support and clinical practice. Educational sessions are interspersed with social events at which members meet and

mingle with Scripps Research trustees, senior management, and scientists.

Throughout the year, members are invited to Scripps Research laboratories, in California and in Florida, to see firsthand how Scripps Research makes science history and helps make medicine's future.

To learn more about The Scripps Council of 100, in California, please contact Denise M. Scalzo, vice president, Development, at (858) 784-9365 or scalzo@scripps.edu. Outside California, please contact William E. Ray, Ph.D., vice president, External Affairs, at (561) 656-6401 or willray@scripps.edu.

1,000 FRIENDS OF SCIENCE

Members of 1,000 Friends of Science support The Scripps Research Institute by gifts from individuals or couples of \$1,000 or more a year.

Members receive the following:

- An annual report outlining the impact of the member's gift,
- An invitation for two to the annual 1,000 Friends of Science Dinner, held on campus in California,
- Invitations and reserved seating for quarterly lectures and receptions called *Frontiers of Science* (in California) and *Frontiers in Scripps Science* (in Florida),
- Invitations to informal quarterly lunches with scientists on campus in California,
- *Endeavor*, Scripps Research's quarterly magazine, and *Scripps Discovers*, a quarterly newsletter for donors.

In addition, there are special benefits for annual contributors at the following levels. Along with 1,000 Friends of Science, they are recognized by giving level in the annual report issue of *Endeavor*.

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

To learn more about opportunities and benefits for annual giving, please contact Wil Burfitt, development officer for annual giving, at (858) 784-2037 or burfitt@scripps.edu.

To learn about opportunities for special gifts restricted for a particular disease, research area, or fellowships and scholarships, please contact Roz Hodgins, development officer for foundations and major gifts, at (858) 784-8274 or hodgins@scripps.edu.

THE SCRIPPS LEGACY SOCIETY

The Scripps Legacy Society is composed of individuals who have made The Scripps Research Institute a beneficiary in their estate plans, including 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.

Members receive invitations for two to the annual Scripps Legacy Society luncheon, held in California, along with subscriptions to *Endeavor*, *Scripps Discovers*, and reserved seating at *Frontiers of Science* events. We are happy to honor any donor's request to remain anonymous.

For more information about becoming a member of The Scripps Legacy Society, please contact Cheryl H. Dean, planned giving counsel, at (858) 784-2380 or cdean@scripps.edu.



Philanthropy Provides the Margin of Excellence

From the organization's founding in 1961, science at The Scripps Research Institute has been characterized and supported by a culture of excellence, innovation, and entrepreneurial independence from traditional boundaries.

In many ways, it is an institution without symbolic walls, encouraging collaboration by its scientists, both on campus and off; freeing them to follow their research wherever it leads, without the burden of excessive bureaucracy; and stimulating spin-off activities, particularly in biotechnology, which bring biomedical discoveries to market—and to clinical practice—more quickly and more efficiently than in the past.

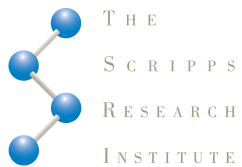
From the start, private philanthropy has helped pave the way for this path of innovative independence.

Proudly, The Scripps Research Institute has maintained its preeminent position among its independent academic institutional peers in annual funding by the National Institutes of Health. But with government support come government rules.

Annually, the portion of Scripps Research's budget provided by gifts, investment income, and royalties also provides the margin of excellence and innovation, which would be unattainable in a more traditional, less entrepreneurial environment.

The portion of Scripps Research's support provided by private individuals and foundations funds the margin of greatness that continues to produce breakthrough basic research, novel drugs and diagnostics, and cross-disciplinary programs—such as the Institute for Childhood and Neglected Diseases—that focus on disease clusters, disease populations, and disease prediction, diagnosis, and therapy.

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



THE
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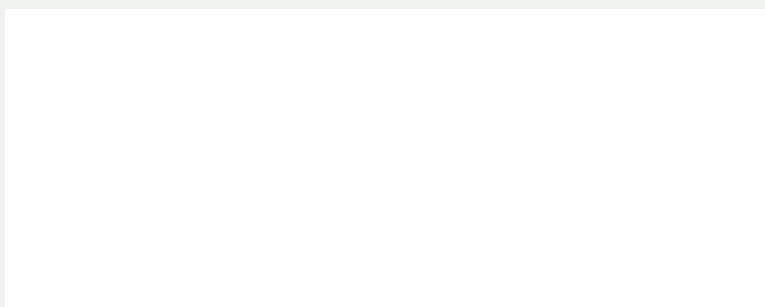
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