

THE SCRIPPS RESEARCH INSTITUTE

# ENDEAVOR

*Breakthroughs of 2008*



WITH  
SPECIAL  
EDUCATION  
SECTION

THE SCRIPPS RESEARCH INSTITUTE

# ENDEAVOR

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ENDEAVOR IS A PUBLICATION OF  
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This issue of *Endeavor* features some of the many scientific breakthroughs of 2008 from investigators at The Scripps Research Institute.



Richard A. Lerner, M.D.  
*President*

## *Year in Review : 2008*

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01

PRESIDENT'S LETTER

I am proud to report on some of the many accomplishments at The Scripps Research Institute during the last year. Our investigators on both coasts made extraordinary advances in their fields, our education and community outreach programs continued to thrive, and a number of Scripps Research teams won major grants to fund innovative projects going forward.

PRESIDENT'S LETTER



*Several Scripps Research teams won large grants in 2008. One \$80 million grant will fund the Molecular Screening Center.*



*Left: Eric Topol, M.D.  
Right: Dennis Burton, Ph.D.*

#### NEW GRANTS BUILD ON ACCOMPLISHMENTS

Despite the difficult funding environment for science in general, Scripps Research teams won several large federal grants in 2008, building on our cornerstone strengths of scientific excellence and interdisciplinary collaboration. These grants are a validation of the quality of our scientists' work on the La Jolla, California, and Jupiter, Florida, campuses.

The largest federal grant in 2008—and in the history of the institute—was an \$80 million award to expand our scientists' efforts to screen molecules for possible drug development at the Scripps Research Molecular Screening Center. The six-year grant from the National Institutes of Health (NIH) to the Scripps Research Molecular Screening Center aims to uncover “proof-of-concept molecules” that could bring closer to reality new treatments for a large number of human diseases. Led by Professor Hugh Rosen, M.D., Ph.D., the group will use Scripps Florida's high throughput robotics to test discoveries made in laboratories in La Jolla and Jupiter, as well as at other research institutions, against various biological targets.

The NIH also awarded \$20 million to the Scripps Translational Science Institute (STSI), a collaborative program between Scripps Research and Scripps Health, partnering with a number of institutions in San Diego. The grant, a Clinical and Translational Science Award, aims to accelerate the translation of scientific discoveries to improvements in medicine. In addition to funding studies relevant to developing individualized treatment and prevention strategies, the grant will support advanced research training. Led by Eric Topol, M.D., STSI is one of only four California programs to receive this type of funding and the first in Southern California.

Through its National Institute of Neurological Disorders and Stroke, the NIH awarded \$7.6 million to investigators at Scripps Florida to develop the next generation of medication to treat Parkinson's disease. The new five-year grant, led by Philip LoGrasso, Ph.D., associate professor and senior director for drug discovery, aims to bring the potential treatment to the point where an ap-

plication can be filed for an investigational new drug—the first step in the lengthy clinical trials process required by the U.S. Food and Drug Administration.

Through its National Institute of Drug Abuse, the NIH awarded \$4 million to a group of investigators on the California campus for research on the effects of chronic marijuana use, including influence on brain function and the consequences of withdrawal. The new Translational Center on the Clinical Neurobiology of Cannabis Addiction, led by Barbara Mason, Ph.D., professor and co-director of the Pearson Institute for Alcoholism and Addiction Research, aims to help develop novel approaches to the prevention, diagnosis, and treatment of marijuana addiction.

#### PRIVATE FUNDING EXTENDS RESEARCH

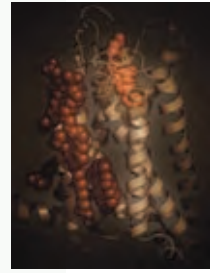
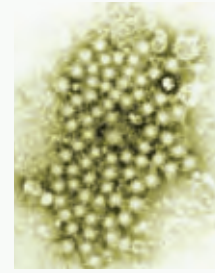
Thanks to the generosity of a number of individuals and foundations, Scripps Research also received noteworthy support from the private and non-profit sectors in 2008, accelerating the progress of our research.

The International AIDS Vaccine Initiative (IAVI), a global non-profit organization, awarded \$30 million to Scripps Research to create a new research center at the institute, which will be linked to a network of research institutions in Africa, Asia, Europe and the United States. The center, led by Scripps Research Professor and IAVI Neutralizing Antibody Consortium Scientific Director Dennis Burton, Ph.D., will focus on expanding efforts to find the crucial antibody-inducing components necessary to make an effective vaccine against HIV and the deadly disease AIDS.

In another act of generosity and foresight, San Diego philanthropist, businessman, and community leader John J. Moores contributed the first donation, a gift of \$2.1 million, to the institute's new \$50 million initiative to recruit new world-class researchers and to sustain and expand the work of current scientists. Moores, chairman and owner of the San Diego Padres baseball team, has served as a member of the Scripps Research Board of Trustees since 1997 and as chair of the Board since 2006.

## 2008

*Left:* Researchers succeeded in disrupting the production of infectious virus particles that cause hepatitis C. *Right:* Scientists determined the structure of the “caffeine receptor,” illuminating medically important G protein-coupled receptors.



Miami physician, businessman and philanthropist Phillip Frost and his wife, Patricia Frost, an ardent supporter of education and the arts, donated \$1 million to Scripps Florida. In recognition of the Frosts' donation, the foyer of the building that will house laboratories for a key component of Scripps Florida research—making strategic scientific discoveries, then accelerating their development into new drugs and treatments to improve human health—will be named the Frost Lobby.

We are deeply grateful for all of the support we receive. We recognize that gifts and grants make possible our scientists' extraordinary efforts to expand scientific knowledge and improve human health.

### SCIENTIFIC BREAKTHROUGHS

This year's scientific findings from Scripps Research laboratories are, as in years past, extraordinary. Some of these breakthroughs are featured in this issue of *Endeavor*, including the solution of a key structure from the deadly Ebola virus, the discovery of a gene linked to Fragile X syndrome, the identification of specific features of neurons that are critical components of the learning process, and the discovery of a gene essential for hearing and balance. To mention a few more of the many important advances made in 2008, Scripps Research scientists:

- + *Reversed Huntington's disease symptoms in mice.* There is no cure for Huntington's disease, or even treatments that can reverse or slow progression of the devastating movement deficits and cognitive dysfunction that occur with the condition. So, it was particularly good news when Assistant Professor Elizabeth Thomas, Ph.D., and colleagues showed an agent that they developed has dramatic therapeutic efficacy in experimental mice, with minimal toxicity. The compound has been licensed for further testing and development.
- + *Found potential new targets for sepsis.* Professor Wolfram Ruf, M.D., and colleagues uncovered a connection between blood coagulation and the immune system that may have important implications for people with sepsis, a severe and difficult to treat disease that kills tens of thousands of Americans a year. The scientists identified a new cross talk involving the vascular coagulation system and

certain cells in the immune system. By disrupting this cross talk, they were able to rescue mice from death due to sepsis.

- + *Devised an approach that stops HIV at the earliest stage of infection.* Professor Chi-Huey Wong, Ph.D., and colleagues developed a new two-punch strategy against HIV and successfully tested aspects of it in the laboratory. The investigators created devices they call glycodendrons that are designed to do two things at once: inhibit the transport of HIV from where it traditionally enters the body, preventing it from moving deeper inside where it can infect immune cells; and set up an immune antibody response to a unique carbohydrate structure on the surface of the virus.
- + *Identified a potential new target for treating metastatic cancer.* Professor James Quigley, Ph.D., and colleagues identified a human protein that may be a new target for future cancer therapies. By experimentally blocking the action of this protein, called CD151, the team showed they could stop cancer cells from metastasizing, or spreading from one tumor to establish new tumors elsewhere.
- + *Developed a process to disrupt hepatitis C virion production.* Timothy Tellinghuisen, Ph.D., an assistant professor at Scripps Florida, and his colleagues discovered a method to disrupt the production of infectious virus particles that cause hepatitis C, a blood-borne liver disease. This discovery might be a first step in developing new and more effective therapies against the hepatitis C virus. Current anti-virals are ineffective for many patients infected with the viral strains most prevalent in the United States.
- + *Defined the structure of an important neurological receptor, establishing a platform to understand G protein-coupled receptors.* Professor Raymond Stevens, Ph.D., and colleagues determined the structure of the human A2A adenosine receptor—sometimes referred to as the “caffeine receptor”—which falls in the larger and medically important family of G protein-coupled receptors. The findings could lead to the development of a new class of therapeutics for treating numerous neurological disorders, including Parkinson's and Huntington's disease.
- + *Devised an innovative method to produce a highly sought-after drug.* Professor Phil Baran, Ph.D. and colleagues developed an inexpensive and in many ways astonishing new method for economically producing a promising pharmaceutical steroid. The molecule, called cortistatin A, which was isolated in 2006 from a marine sponge, has shown huge promise for treating conditions ranging from macular degeneration to cancer.



After the 2008 commencement ceremonies, the Kellogg School can boast of more than 300 distinguished alumni, including Chan Woo Huh (right), shown here with his advisor and Florida dean William R. Roush.



Albert Eschenmoser, Ph.D.



Jeffery Kelly, Ph.D.

- + *Created the first successful libraries of avian flu virus.* Working with an international team including researchers at Sea Lane Biotechnologies, I created the first comprehensive monoclonal antibody libraries against avian influenza (H5N1) using samples from survivors of the 2005/2006 “bird flu” outbreak in Turkey. These antibody libraries hold the promise for developing a therapy that could stop a pandemic in its tracks and provide treatment to those infected, as well as potentially pointing the way towards the development of a universal flu vaccine.
- + *Uncovered a new catalytic antibody that might be used to fight obesity.* Kim Janda, Ph.D., Scripps Research professor and member of the Skaggs Institute, Eric Zorrilla, Scripps Research associate professor, and colleagues discovered a catalytic antibody that degrades a known appetite stimulant. The antibody works against the gastric hormone ghrelin, which has been linked to weight gain and fat storage. These findings point towards a potentially novel treatment for obesity.

#### COMMITMENT TO EDUCATION

In addition to our dedication to research, Scripps Research is committed to educating the next generation of scientists, and a section in this issue of *Endeavor* provides details about many of our activities on this front.

To mention a few highlights, our commencement ceremony in May graduated 28 Ph.D. candidates from the Kellogg School of Science and Technology and recognized Scripps Research trustee Claudia S. Luttrell with an honorary degree.

The school can now boast of more than 300 accomplished alumni. Three alumni—two from this year’s graduating class—conducted their studies on the Scripps Florida campus.

The fall brought a record number of entering graduate students to both campuses. At Scripps Florida, an unprecedented 75 percent of offers extended to students were accepted—nine of 12 offers made. Of these nine students, four come from Florida universities.

In addition, we continue to build programs to support our valued postdoctoral fellows, and to make strides reaching out to high school students and teachers to share our excitement about the scientific endeavor.

#### PEOPLE NEWS

The year brought a variety of transitions for people at the institute.

We welcomed international business leader and entrepreneur Amin J. Khoury to the Scripps Research Board of Trustees. Khoury, who is chair of the Board and chief executive officer of B/E Aerospace, Inc., of Wellington, Florida, brings to the board his talents as a business executive and his experience as founder of companies in aerospace, as well as the scientific instrument, medical services, and medical devices fields.

Roy Smith, Ph.D., joined Scripps Florida from Baylor College of Medicine to head our new Department of Metabolism and Aging. I look forward to his contributions to this exciting field, which is advancing our knowledge of aging and age-related diseases.

Hollis Cline, Ph.D., joined the California campus as part of the institute’s Departments of Cell Biology and Chemical Physiology. Cline’s expertise in the neuroscience of vision will be a significant contribution to the world-class neuroscience research at the institute.

Professor Jeanne F. Loring, Ph.D., renowned in the field of stem cell research, joined the faculty at Scripps California. Loring will apply her extensive knowledge and experience to lead a team to new discoveries that will benefit human health.

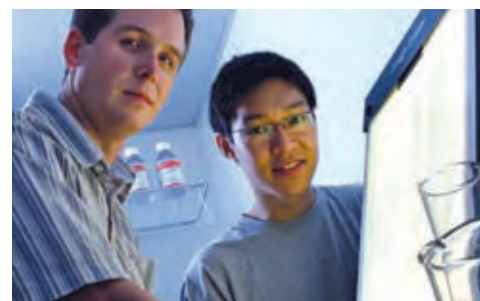
Richard Ulevitch, Ph.D., an internationally renowned researcher in the field of innate immunity, stepped down as chair of the Department of Immunology this year. He is continuing to maintain a laboratory at Scripps Research as professor and chair emeritus while joining 5AM Ventures of Menlo Park, California. Professor Argyrios Theofilopoulos, M.D., is acting chair as we conduct an international search to fill this position.

Ernest Beutler, M.D., chair of the Department of Molecular and Experimental Medicine (MEM) since 1978, stepped down from this role in 2008. Filling the position is Jeffery Kelly, Ph.D., Lita Annenberg Hazen Professor of Chemistry and a member of the Scripps Research Skaggs Institute of Chemical Biology, who also recently became chair of the Board of Trustees of the



Sandra Schmid, Ph.D.

## Our esteemed faculty again received many honors.



Scripps Research scientists, among them investigator Ian MacRae, Ph.D., (left) and graduate student Pick-Wei Lau, continue groundbreaking research at the intersection of chemistry and biology.

Skaggs Institute for Research (one of the Skaggs family's major mechanisms for its philanthropy). It is with great sadness I report that Ernie Beutler, who was planning to continue to run his research program, passed away in October. His passing is a great loss to science, to the institute, and to all who knew and worked with him over his long, brilliant career. [See *In Memoriam*, page 35.]

Assuming the deanship of the Kellogg School from Jeff Kelly is Professor Jamie Williamson, Ph.D., also a member of the Skaggs Institute, who will build on his seven years as associate dean and decade as a Scripps Research faculty member to lead this top-ranked graduate program into the future.

### FACULTY HONORS

In 2008, our esteemed faculty again received many honors and awards. To name just a few:

- + Three of our colleagues—Bruce Beutler, M.D., Mike Oldstone, M.D., and Peter Wright, Ph.D.—were acknowledged for their outstanding research achievements by election to the National Academy of Sciences. That brings to 19 the number of National Academy members among our faculty. To have had three such deserving researchers elected in one year is truly remarkable for an organization of our size.
- + Professor Albert Eschenmoser, Ph.D., won the Benjamin Franklin Medal in Chemistry. Franklin Institute Awards are given for outstanding achievements that have enhanced the quality of human life and deepened our understanding of the universe; Eschenmoser was recognized for his research on nucleic acid structure, leading to the understanding of why RNA and DNA have the structure they do.
- + Professor Ian Wilson, D. Phil., was showered with honors, including an honorary degree from the University of St. Andrews in recognition of achievements “at the forefront of research to understand the immune system and influenza”; election as a Corresponding Fellow of the Royal Society of Edinburgh, Scotland's National Academy of Science and Letters; and election to the Board of Directors of the Keystone Symposia.
- + Professor Carlos Barbas III, Ph.D., was selected to receive the 2009 Tetrahedron Young Investigator Award, Biorganic &

Medicinal Chemistry, an award for individuals under the age of 45 who have exhibited “exceptional creativity and dedication” in their fields. In addition, Barbas was chosen for the American Chemical Society Arthur C. Cope Scholar Award, which recognizes excellence in the field of organic chemistry.

- + Jeffery Kelly won the American Peptide Society's Vincent du Vigneaud Award, sponsored by Bachem, Inc., for “fundamental, visionary research on folding and aggregation processes in peptides and proteins, and for courageous, insightful exploration of the biological and medical implications of his discoveries.”
- + Sandra Schmid, Ph.D., chair of the Department of Cell Biology, was chosen by the American Society for Biochemistry and Molecular Biology to receive the William C. Rose Award, which recognizes outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists.
- + Associate Professor Gaudenz Danuser, Ph.D., won the Michael & Kate Bárány Award for Young Investigators from the Biophysical Society for his “outstanding seminal contributions in diverse areas of cell biology, particularly to our understanding of cell cytoskeleton dynamics and function using speckle microscopy.”
- + Assistant Professor Ian MacRae, Ph.D., was selected as a 2008 Pew Scholar in the Biomedical Sciences by the Pew Charitable Trusts and the University of California at San Francisco. MacRae will receive four years of support for his research, which combines structural biology, biochemistry, and cell biology to understand mechanisms of gene regulation by RNA interference.

As we look forward to celebrating the opening of the permanent Scripps Florida campus in February 2009, I am delighted to take this moment to appreciate the many, significant accomplishments that have brought us this far. Thank you to trustees, donors, friends, faculty, staff, postdoctoral fellows, and students of Scripps Research for your dedication, hard work, and vision.

Sincerely,

Richard A. Lerner, M.D.



Sites of previous Ebola outbreaks.

## Out of Africa

ERICA OLLMANN SAPHIRE TAKES THE PATH LESS TRAVELED WITH EBOLA

Last March, Erica Ollmann Saphire, Ph.D., journeyed to Libreville, the capital of the West African state of Gabon, to meet with more than 100 of her fellow research specialists from around the world. It was Ollmann Saphire's first time in Africa, and just a few short months before she had made headlines as the woman who broke open the secrets of the Ebola virus, one of two main types of deadly filoviruses (the other being Marburg virus) that originate in the jungles of Central Africa.

At the time of her visit, Saphire was in the final stage of a five-year research gamble to uncover the structure of a key protein that resides on the surface of the Ebola virus and allows it to enter human cells. Over those five years, Ollmann Saphire and her team, including Research Associate Jeffrey Lee, Ph.D., and Research Assistant Marnie Fusco, produced more than 50,000 crystals, expressed 140 versions of the Ebola virus glycoprotein, and made more than two dozen synchrotron trips to throw x-rays at the crystal, all as part of the team's use of a technique called x-ray crystallography. Despite its major drawback—that the material under study must be in a crystal form—x-ray crystallography still sets the gold standard for determining the atomic structure of molecules.

"The Ebola virus proteins have been hard to work with," says Ollmann Saphire. "They are heterogenous and unstable and don't want to be

crystallized. Plus, the virus itself is so difficult and dangerous to work with that most of the experiments you would want to do just can't be done easily. So, any success you do have can dramatically advance the field and have a major impact on possible treatments."

The 36-year-old Scripps Research scientist's breakthrough study, which appeared as the cover article of the July 10, 2008, issue of the journal *Nature*, finally lifted the veil from the virus's spike-shaped protein, a critical step in understanding how Ebola works and an essential step for any potential development of a treatment or vaccine.

"Much about Ebola virus is still a mystery," says Ollmann Saphire. "However, this structure now reveals how this critical piece of the virus is assembled and, importantly, identifies vulnerable sites that we can exploit."

### A FORMIDABLE FOE

Although relatively rare—there have been fewer than 30 known outbreaks of Ebola and around 1,200 human deaths since it was first identified in 1976 in Zaire—the Ebola virus is not to be trifled with.

There is currently no cure for Ebola hemorrhagic fever, which inflicts a death rate as high as 90 percent of those infected. Most often spread →





when people come into contact with the bodily fluids of an infected individual, symptoms start with a sudden fever, then swiftly progress to muscle pain, headache, and sore throat, followed by vomiting, diarrhea, rash, and kidney and liver failure. In the final stages, massive hemorrhaging causes heavy bleeding from body openings and internal organs.

The best treatment consists of administering fluids and taking protective measures to ensure containment, like isolating the patient and washing sheets with bleach.... or burning them.

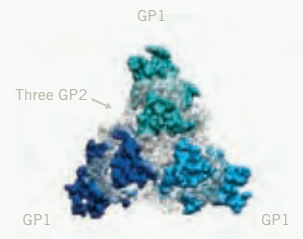
With its high mortality rate and gruesome symptoms, the virus has captured some attention. A hair-raising account of a 1989 outbreak of Ebola at a research facility near Washington, D.C., was chronicled in Richard Preston's international best-seller, *The Hot Zone: A Terrifying True Story*. The book, published in more than 30 languages, has sold some 2.5 million copies worldwide.

While thankfully still rare in humans, Ebola seems to be devastating other primate populations in Central Africa. One study, published in 2006 in the journal *Science*, estimated that the Ebola virus, with a 90 to 95 percent mortality rate among gorillas, had killed more than 5,000 of these creatures at a single site in West Africa. One of the study's authors suggested that Ebola was responsible for the death of one quarter of the world's gorilla population during the previous 12 years.

#### "OUR WITS VERSUS THEIR GENES"

Ollmann Sapphire, who was born in Baton Rouge, Louisiana, but grew up in Austin, Texas, often speaks of Ebola in a kind of anthropomorphic shorthand, as a "ferocious little beast" she vividly describes with evenly matched bits of high and low culture.

Two views show the Ebola virus spike protein, which is necessary for viral entry into human cells, bound to an immune system antibody acting to neutralize the virus.



"I sometimes think of Ebola as something out of "Spy vs. Spy," you remember the old *Mad Magazine* cartoon?" she says. In that minimalist cartoon strip, two pointy beaked spies, one black and one white, try to kill each other wordlessly in typical Rube Goldberg fashion, constructing elaborate instruments of destruction—the Itchy & Scratchy of their time.

On the other hand, one of her favorite quotes about viruses comes from Joshua Lederberg, Ph.D., the 1958 Nobel laureate: "The future of humanity and microbes will likely unfold as episodes of a suspense thriller that could be titled 'Our Wits versus Their Genes.'"

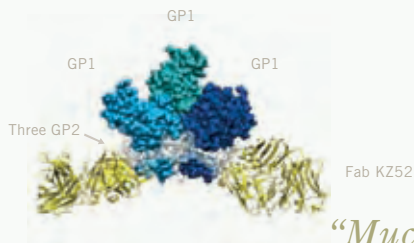
But there's nothing mythical about viruses, she says, they're more like fellow travelers along for the same ride as the rest of us. "Viruses are here to propagate themselves just like us," she says. "Basically, we're competing for the same resources."

Ollmann Sapphire's latest study was a victory for our side.

The Ebola virus glycoprotein itself, the one thing that is necessary for attaching to and infecting a host, has been a therapeutic target for more than 10 years. But because the structure was unknown, no one knew how to take advantage of it.

The glycoprotein comes covered in what has been described as a "cotton candy coating" of jumbled proteins and carbohydrates, which helps stabilize the virus and enables it to escape the immune system by keeping the all-important binding mechanism hidden.

The structure solved by the lab showed the few surface sites not hidden by that carbohydrate-protein coating, and explains how the molecules assemble on the Ebola viral surface and how the pathogen evades the human immune system. The structure also gives researchers targets to aim for



*“Much about Ebola virus is still a mystery. However, this structure now reveals how this critical piece of the virus is assembled and, importantly, identifies vulnerable sites that we can exploit.”*

ERICA OLLMANN SAPHIRE, Ph.D.

in developing any potential therapeutic.

“Those sites are chinks in the virus’s elaborate armor that we can target antibodies against,” says Ollmann Saphire. “In fact, the structure has already been quite useful in helping us elicit and combine new types of antibodies.”

#### FIGURING THINGS OUT

Ollmann Saphire wanted to be a journalist in high school because it meant seeing new things, maybe experiencing some adventure, and having a decent chance to figure things out. Her parents were teachers and she remembers that they often spent their summers traveling to national parks. In college at Rice University in Houston, Texas, where she first took up science, she was also on the editorial board of the campus newspaper and wrote what she calls comic relief—after a day in the laboratory she didn’t want to write anything too serious.

She was never afraid of failure in her laboratory work, but instead tried to figure out why the experiment didn’t work, what the next step might be, and how she could somehow make it better. The whole process of biology, of experimentation itself, seemed satisfying to her in ways she could not totally explain.

It’s no wonder, then, that she continued to pursue science in graduate school. Working in the Scripps Research laboratory of Professor Ian Wilson, she took on a difficult and ambitious project involving another infamous and deadly virus—human immunodeficiency virus (HIV)—as part of a larger effort to help develop a vaccine against AIDS.

The team, which also included Scripps Research Professor Dennis Burton, was attempting to solve the structure of one of the few antibodies

(specific immune system molecules) known to help fight off HIV. The antibody had originated in the bone marrow of a 31-year-old male who had been HIV positive without symptoms for six years.

Ollmann Saphire began work in 1994—with the sobering knowledge that others had previously tried to crystallize b12—a necessary step in solving the structure—but had given up. She worked for four years on the project without notable progress.

Then, in August 1998, out of what she described as “sheer desperation,” the team tried a different tack. Instead of breaking the antibody into fragments and trying to crystallize the fragments—the classic antibody approach—the scientists attempted to crystallize the antibody in its entirety, despite the fact that no one had ever crystallized a whole human antibody before.

Amazingly, it worked.

The team went on to publish the structure of b12 in the journal *Science*, describing how the antibody has a long finger-like region on its surface that grips the surface of the HIV virus and prevents it from causing disease.

Ollmann Saphire graduated from what is now the Scripps Research Kellogg School of Science and Technology in 2000, and chose to stay at Scripps Research where she now heads her own lab. While she still collaborates with Wilson and Burton, her primary focus has shifted from the study of HIV to pathogens causing viral hemorrhagic fevers, namely Lassa and Ebola.

#### HEART OF DARKNESS

Ollmann Saphire’s penchant for figuring things out still extends beyond the lab, though. This fact might help explain why, before the recent con-

*“Viruses are here to propagate themselves just like us. Basically, we’re competing for the same resources.”*

ERICA OLLMANN SAPHIRE, Ph.D.

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OUT OF AFRICA



Transmission electron micrograph of Ebola virus, courtesy of the Centers for Disease Control and Prevention.

ference in Libreville, she and her 64-year-old administrative assistant, Ellen Klahn, set off by train across the jungle. They had only a few words of French, Gabon's official language, between them.

After fending off at-gunpoint demands for money from the local police on the train, they met their guides, former trackers and hunters who spoke little or no English, and set out to experience Ebola's natural habitat—the rainforest where temperatures hover around 95 degrees and humidity at the same level. This is the type of jungle that is always described as “impenetrable,” the same jungle where Joseph Conrad set *Heart Of Darkness*, his classic novel of Africa, which he describes as “like traveling back to the earliest beginnings of the world.”

“It was an opportunity to see where Ebola lives,” Ollmann Saphire says. “In the lab we're so reductionist, we look at molecules. But these molecules are made this way so they can live in a hot, sticky rainforest or a cave. To understand why they are the way they are, you have to see them in nature.”

In the jungle, the group walked silently for two weeks, wearing long sleeves and bandanas to keep the bugs away, waiting for the moment when an animal would appear—something that might give them a better picture of how Ebola spreads. Based on seroreactivity among the wild animal population, Ollmann Saphire was confident there were Ebola viruses circulating in places like this where there has never been a human outbreak. The viruses lurk in the bats and primates, who share food, like the pieces of fruit that drop from the trees.

“The fruit bats peck at it, it falls to the ground, a gorilla eats some, and elephants finish off the rest,” Ollmann Saphire notes. “You can see how the virus gets spread and incubated in the wild.”

Not surprisingly, she is planning to head back to Africa soon, this time to visit a hospital with which her lab is collaborating on investigations of the virus that causes Lassa hemorrhagic fever.

#### POWERED BY PERSISTENCE

Now back in the lab, Ollmann Saphire is employing her trademark perseverance against new problems related to Ebola and other hemorrhagic fevers, with her experience in jungles of Africa to inform her.

Her basic approach in the lab (as in the jungle) is very much akin to a foot soldier in a long campaign—no one can afford to give up, so there is no other option but to keep going.

“What we do is difficult, so when I hire people I always look to see how steely and resilient they are,” she says. “There is *always* the possibility of failure; that's built into the nature of the work. So, after a bad day, you go home, have a glass of wine, do some soul searching, and then come up with a new idea on how to defeat it.”

The recent spurt of scientific fame that followed her Ebola breakthrough is a rare, although appreciated, moment of glory.

“We toil in obscurity, so when we succeed like this, we can show the taxpayers, who fund our work, what their investment can do,” she says.

ERIC SAUTER AND MIKA ONO





*“In my work, I am driven by a basic curiosity about how we fight infections and how the innate immune system allows us to survive them.”*

BRUCE BEUTLER, M.D.



## Moving Genetics Forward

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BRUCE BEUTLER DISCOVERS THE BEAUTY OF CALCULATED SURPRISES

Bruce Beutler, M.D., is at a point in his life when he can look to the past to help see the future.

“I remember as a child being very interested in nature, really wondering about what it was that made animals alive,” he says. “My father encouraged this kind of curiosity, but he pushed me to be more experimental, and not merely observational.”

Now, many years later, Bruce Beutler is a renowned investigator at The Scripps Research Institute, where he chairs the Department of Genetics and where his father, the late Ernest Beutler, M.D., led the Department of Molecular and Experimental Medicine for more than 30 years.

Bruce credits his father with passing on some key lessons that have shaped his scientific pursuits. It was, in fact, in his father’s lab that Bruce was first introduced to research. There, about 35 years ago, he learned to assay red cell enzymes, purify them, and analyze them by electrophoresis. He and his father published two papers together at that time, dealing with mutations that affect the activity of one such enzyme: glutathione peroxidase.

Bruce Beutler subsequently found a big question to tackle. “In my work, I am driven by a basic curiosity about how we fight infections and how the innate immune system allows us to survive them,” he says. Then, in language that echoes the boy he was, he adds, “I think of microbes as very elegant

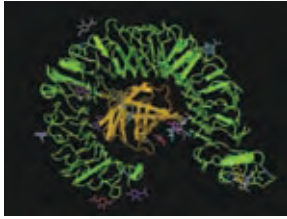
little machines, and I think of humans, and mice, as very elegant big machines that have evolved ways of opposing these infections.”

He has also found a unique way to find answers, adapting an old idea to modern techniques. The method, called “forward genetics,” is in many ways a state-of-the-art throwback to Mendelian genetics, which starts with phenotype, the observable characteristics of each individual, to find clues about the inner workings of inherited traits.

This approach has led Beutler to a number of seminal contributions to the field, including several groundbreaking studies published just this year, one co-authored with his father.

### THE POWER OF FORWARD GENETICS

At the time Bruce Beutler first embraced forward genetics, he was a 35-year-old investigator at the University of Texas Southwestern Medical Center in Dallas. He had been in a rush to become a researcher: he had graduated from the University of California, San Diego, at age 18, in just two years, then earned his M.D. from the University of Chicago, interned, and completed his residency at the Southwestern Medical Center. He had chosen medical school on the advice of his father, who said it would give him a broad scientific education. →



TLR4 (green) and MD-2 (yellow) act together as the mammalian LPS sensor. The lipid part of LPS is bound in a pocket of MD-2, and a resulting shape change is communicated to the “horseshoe-shaped” TLR4 protein, causing it to signal, and alerting the host to the presence of infection. Beutler and his group discovered the function of TLR4 by positional cloning. The structure of the TLR4-MD-2 complex was later solved by H.M. Kim, et al (*Cell* 130:906-917, 2007)

It did, and it also fueled his desire for laboratory investigation.

Beutler then headed off to Rockefeller University in New York City for a postdoctoral fellowship. There, he made his mark by isolating mouse tumor necrosis factor (TNF), which was known to kill tumor cells, but which Beutler showed to be critical to the body’s response to infections—especially in its ability to cause shock induced by endotoxins, toxins produced by certain bacterial pathogens and released upon destruction of the bacterial cell. He later invented molecules that could neutralize TNF, an advance that formed the basis of the drug Etanercept, which is used for the treatment of rheumatoid arthritis, Crohn’s disease, psoriasis, and other inflammatory conditions.

When he returned to Southwestern Medical Center as a Howard Hughes Medical Institute investigator, he tackled the next logical question—how does endotoxin (lipopolysaccharide, or LPS) activate mammalian cells? This question was a big one in immunology, because LPS had been known for many decades to mimic infection, yet nobody understood precisely how it was sensed. Nor, for that matter, was much known about how any microbes (bacteria, fungi, or viruses) were initially sensed by the host in order to trigger an appropriate immune response.

At first, Beutler tried to locate the receptor for LPS using traditional tools of molecular biology and biochemistry, but he finally concluded it “absolutely could not be found with these techniques.”

There was, however, a phenotype that offered a clue: a particular strain of mice had genetic mutations that made them resistant to inflammatory shock and the effects of LPS.

“I decided to drop everything else and positionally clone this gene,” he says. “That’s what we did, and I began to see how powerful the method was.”

In positional cloning, a.k.a. forward genetics, scientists identify an interesting phenotype, then use modern laboratory techniques to identify the exact location of the responsible mutation on the chromosome.

In all, it took Beutler and his group five years to find the mutation that caused resistance to LPS, but the results were trailblazing. The scientists found that the protein encoded by a gene named *Tlr4* (Toll-like receptor 4) detects LPS and triggers the production of cytokines (including TNF) that orchestrate inflammation and provide an immediate defense against infection.

The finding revealed how we detect Gram-negative infections, and shed light on the larger issue of how we sense all microbes.

#### UNBIASED CURIOSITY

In his laboratory at Scripps Research, where he arrived in 2000, forward genetics continues to be central to Beutler’s success.

His research program uses mutagens to create great numbers of gene mutations in mice, and a breeding plan that tracks and amplifies these



*“I decided to drop everything else and positionally clone this gene. That’s what we did, and I began to see how powerful the method was.”*

BRUCE BEUTLER, M.D.

mutations through several generations. Beutler’s is the largest mouse mutagenesis laboratory in the world and one of the few that uses forward genetics to understand innate immunity.

Beutler says that the beauty of using forward genetics is that it is calculated to produce surprises. The method starts with observation and with an unbiased curiosity about a phenomenon.

“With this approach, I have no idea what genes I will find,” he says.

The genes he has found so far have revealed some fascinating information about the inner workings of our biology.

On the topic of innate immunity, Beutler and his colleagues have established many of the essential proteins that are active in TLR signal transduction, although many others remain to be found.

His work points to an image of innate immunity that is remarkable for its simplicity and power. Just a few dozen proteins help humans protect themselves against hundreds of thousands of microbes by recognizing just a few of their products, be it double-stranded RNA or DNA or single stranded DNA, flagellin, lipopolysaccharides, or lipopeptides.

“In short, we’ve developed ‘one-size-fits-all’ mechanisms by which we recognize not just one microbe species but many microbe species,” he says. “With only 10 Toll-like receptors, we can recognize almost all of the microbes that are out there, and that is simply amazing.”

Beutler is now extending his research in this area to explore to what extent the Toll-like receptor system contributes to inflammatory and autoimmune diseases, as well as to cancer.

#### NEW TERRITORY

Forward genetics has also led Beutler into unexplored territory, with pioneering new insights.

In 2008, Beutler published a study with his Scripps Research colleagues Staff Scientist Xin Du, Ph.D., Professor Ulrich Mueller, Ph.D., Senior Research Associate Martin Schwander, Ph.D., and Chair of the Committee on Neurobiology of Addictive Disorders George Koob, Ph.D., announcing the discovery of a gene that is essential for both hearing and balance in mice and humans.

While most hereditary deafness is caused by alterations of structural proteins in the inner ear, this gene instead encodes an enzyme with a known catalytic function, hinting that the problem might be preventable with novel drug therapy.

The paper, published in the *Proceedings of the National Academy of Sciences* in September, resulted from a mouse that turned up in Beutler’s forward genetics program carrying a mutation that caused deafness, hyperactivity, and balance problems. When the scientists identified the defective gene, they found it was highly expressed in the hair cells of the inner ear. The scientists were then able to identify the equivalent gene in humans, and confirm that some deaf people indeed carry mutations.



Beutler points out that the simplicity of the innate immune system can be likened to the smallest part of an hourglass. Reacting to hundreds of thousands of microbes, just a few dozen proteins in the innate immune system protect us by activating thousands of different genes.

*“Previously, we only knew that structural defects of the hair cells could cause deafness. We were surprised to find that an enzyme for catecholamine inactivation is also required for hair cells to survive.”*

BRUCE BEUTLER, M.D.

The new gene, which the scientists labeled *COMT2*, is a sister to the well-known *COMT* (catechol-O-methyl transferase) gene. Both of these genes encode proteins that degrade catecholamines, key neurotransmitters such as dopamine and norepinephrine, to keep them from accumulating and harming cells that have receptors for them. Defects in the *COMT* gene within the brain have already been linked to development of schizophrenia.

“We think it is possible that when *COMT2* is defective, catecholamines accumulate around the hair cells, which are specialized to interpret sound energy and generate signals to be processed by the brain,” says Beutler. “The catecholamines may then overexcite and damage or kill the hair cells. This is a wholly unexpected finding. Previously, we only knew that structural defects of the hair cells could cause deafness. We were surprised to find that an enzyme for catecholamine inactivation is also required for hair cells to survive.”

He adds that while the researchers suspect that defects in *COMT2* cause only a small percentage of human deafness—mutations in the gene were found in only about two percent of 192 deaf patients in the study—this discovery may lead to new understanding about the role that catecholamines play in other forms of deafness and perhaps in other disorders.

#### REMOVING THE MASK

In another seminal study published in 2008, Beutler and Du led a team that pinpointed an important protein essential for the normal absorption of iron in the body.

“Iron is fundamentally important to all forms of life, but before our study no one knew precisely how higher organisms ‘know’ that they are becoming iron deficient and upregulate iron absorption to correct this condition,” said Beutler. “The findings reveal the first molecular component of a pathway that detects iron deficiency, and helps produce a homeostatic response.”

This research topic was inspired by another “surprise” from Beutler’s forward genetics program, a mouse the scientists dubbed “Mask” because it lost its body hair while retaining facial hair. The Mask mouse proved to have iron deficiency anemia as well, and inappropriately high levels of the hormone hepcidin, a liver peptide that acts as the master regulator of intestinal iron absorption and release of iron from the tissues.

Beutler (left), Yu Xia (center) and Kevin Khovananth (right) monitor the function of a robot that operates in conjunction with a DNA sequencer and high speed computer to find mutations in the mouse genome. Xia, a staff scientist, and Khovananth, a scientific associate, devised this integrated system for mutation finding, which permits positional cloning with unparalleled speed.



*“Understanding host defense mechanisms is beautiful in its own right.”*

BRUCE BEUTLER, M.D.

One notable co-author of the *Science* paper was Ernest Beutler, whom Bruce recruited to work on the study as soon as he realized iron metabolism was involved. “I don’t want to sound like I’m bragging about my father,” Bruce says, “but he was the world’s expert on iron metabolism.”

Published in the journal *Science* in May 2008, the paper that resulted from the effort describes findings that a protein called TMPRSS6, a cell surface protease, suppresses gene expression of hepcidin. Under normal circumstances, body iron content is tightly regulated, and pathways for the increase or suppression of hepcidin are activated in response to iron excess or iron deficiency. The researchers found that a splicing error in the TMPRSS6 gene disrupted normal iron regulation, causing anemia.

“We discovered that the Mask mouse was insensitive to low iron levels and failed to suppress hepcidin production,” Beutler says. “If iron is depleted, the body needs a mechanism to sense the deficiency and to increase iron absorption from the diet. TMPRSS6 turned out to be an essential component of this low-iron detection pathway, one that is independent of previously understood hepcidin gene activation pathways.”

Subsequently, other groups have shown that a number of human patients with iron deficiency anemia refractory to iron supplementation have mutations in the human TMPRSS6 gene.

“Usually,” says Beutler, “genetic diseases in the

mouse have a counterpart in humans, because humans and mice are very similar to one another in their genetic makeup. Genetic studies in mice consistently lead the way to the identification of human genetic diseases that have not been recognized before.”

The TMPRSS6 discovery could lead to novel therapies to block anemia during chronic diseases or to treat hemochromatosis, a genetic disease caused by an overabundance of iron.

#### THROUGH THE GENERATIONS

Around the same time the *Science* paper hit the stands, the National Academy of Sciences announced that Bruce Beutler had been elected as a member of that esteemed organization.

The National Academy election was the latest in a string of honors for Beutler, which have recently included the prestigious Balzan Prize, the William B. Coley Award, the Gran Prix Charles-Leopold Mayer, and the Robert Koch Prize.

Bruce Beutler says that while his work has led—and may continue to lead—to new disease treatments or to strategies to counteract the next pandemic, what keeps him going day to day is more fundamental.

“Understanding host defense mechanisms is beautiful in its own right,” he says. “That’s what makes it worth all the hard work.”

RENEE TWOMBLY AND MIKA ONO



*“I couldn’t help but notice there was so much else in the genome over and above conventional genes and I got fascinated by it—obsessed by it, really—and wanted to find out what was going on.”*

CLAES WAHLESTEDT, M.D., Ph.D.

## Watching the Dark

CLAES WAHLESTEDT FINDS ANSWERS IN UNEXPECTED PLACES

Claes Wahlestedt, M.D., Ph.D., a Scripps Research Institute scientist who heads the Scripps Florida effort to develop drug candidates for diseases of the central nervous system, had two major studies published in 2008, both of them focusing on the remarkable power of noncoding RNA, a power that is becoming increasingly more visible thanks to Wahlestedt’s efforts.

Non-coding RNAs are small molecules that do not produce proteins and that were once thought of as little more than evolutionary leftovers, junk DNA that littered the genome but did nothing of any *real* importance. However, as Wahlestedt’s recent studies have shown, non-coding RNAs play a vital role in gene expression, a process critical to a number of disease states.

There are several different types of non-coding RNA, including microRNA and small interfering RNA (siRNA). MicroRNAs regulate gene expression and have been linked to both cancer and heart disease; siRNA is part of a pathway that inhibits gene expression and is critical to the immune system and how it responds to viral infection.

Wahlestedt’s study in the July 2008 issue of the journal *Nature Medicine* showed for the first time that a specialized form of RNA is directly linked to increased levels of amyloid plaque in the brains

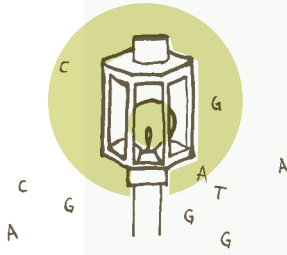
of Alzheimer’s patients. In that study, the scientists identified a noncoding antisense form of RNA that controlled the expression of  $\beta$ -secretase-1 (BACE1), an enzyme critical to Alzheimer’s disease progression.

“Our *in vivo* studies showed that a widely overlooked molecule, BACE1-AS, helps regulate a critical mechanism associated with Alzheimer’s disease, and may turn out to be key to the pathological progression of the disease,” Wahlestedt says.

Another recent study from the Wahlestedt lab, published January 23, 2008, in the online journal *PLoS ONE*, outlined the discovery of a new gene that could be a significant contributor to a leading known cause of autism. The gene, known as FMR4, may contribute to the development of Fragile X syndrome, the most common cause of inherited mental retardation, including such autistic-like behaviors as social anxiety, poor eye contact, and hand biting. Approximately one-third of all children diagnosed with Fragile X syndrome also have some degree of autism, according to The National Fragile X Foundation.

In parallel, Wahlestedt’s group also studies genetic factors that underlie schizophrenia, and he thinks that noncoding RNAs will be important to track in this devastating disorder as well. →





### DARK MATTER

Wahlestedt has been looking at these previously ignored bits of genetic junk for a good portion of his life, even before they reached the status of hot scientific topic.

“In the 90s, the prevailing opinion in the pharmaceutical industry was that once we had the full human genome there would be no more problems for the future,” he says. “The industry in many ways drove the race to determine the DNA sequence of the human genome, and while scientists found some important material, there was also a bit of a disappointment. First off, there were fewer conventional genes than we thought.”

The surprisingly small number of protein coding genes, much like the curious incident of the dog that didn’t bark, piqued his interest.

The genetic puzzle of the last decade or so, Wahlestedt has often said, is the fact that out of the three billion base pairs of DNA in the human genome, only slightly more than one percent of them actually produce proteins. But at the same time, over 90 percent of the genome is active. So what’s going on? What are all these extraneous bits and pieces for?

His two studies this past year, as well as upcoming publications, underscore the growing awareness among scientists not only of the complexity and unpredictability of the human genome, but also of just how important those extraneous parts can be.

“We know now that our genome is very busy and very complicated,” Wahlestedt says. “A great deal of this newfound complexity is about the regulation of other genes. As evolution has moved for-

ward, particularly in the higher organisms, there has been a corresponding increase in the need for regulatory mechanisms—to maintain more control over the genome. As it turns out, non-coding RNAs are at the center of these regulatory mechanisms and nowhere is this more evident than in the human brain.”

In Wahlestedt’s case, he stared into the darkness and the darkness suddenly stared back.

“I couldn’t help but notice there was so much else in the genome over and above conventional genes and I got fascinated by it—obsessed by it, really—and wanted to find out what was going on. So, I left the industry to study it. You see, everybody looks at the protein coding genes to find therapeutic answers, but for me that was like looking for the key by the lamppost. There was so much more out there in the darkness.”

Wahlestedt’s work shows just how much lies in the dark beyond the lamppost—which doesn’t necessarily mean that he’s abandoned the light altogether.

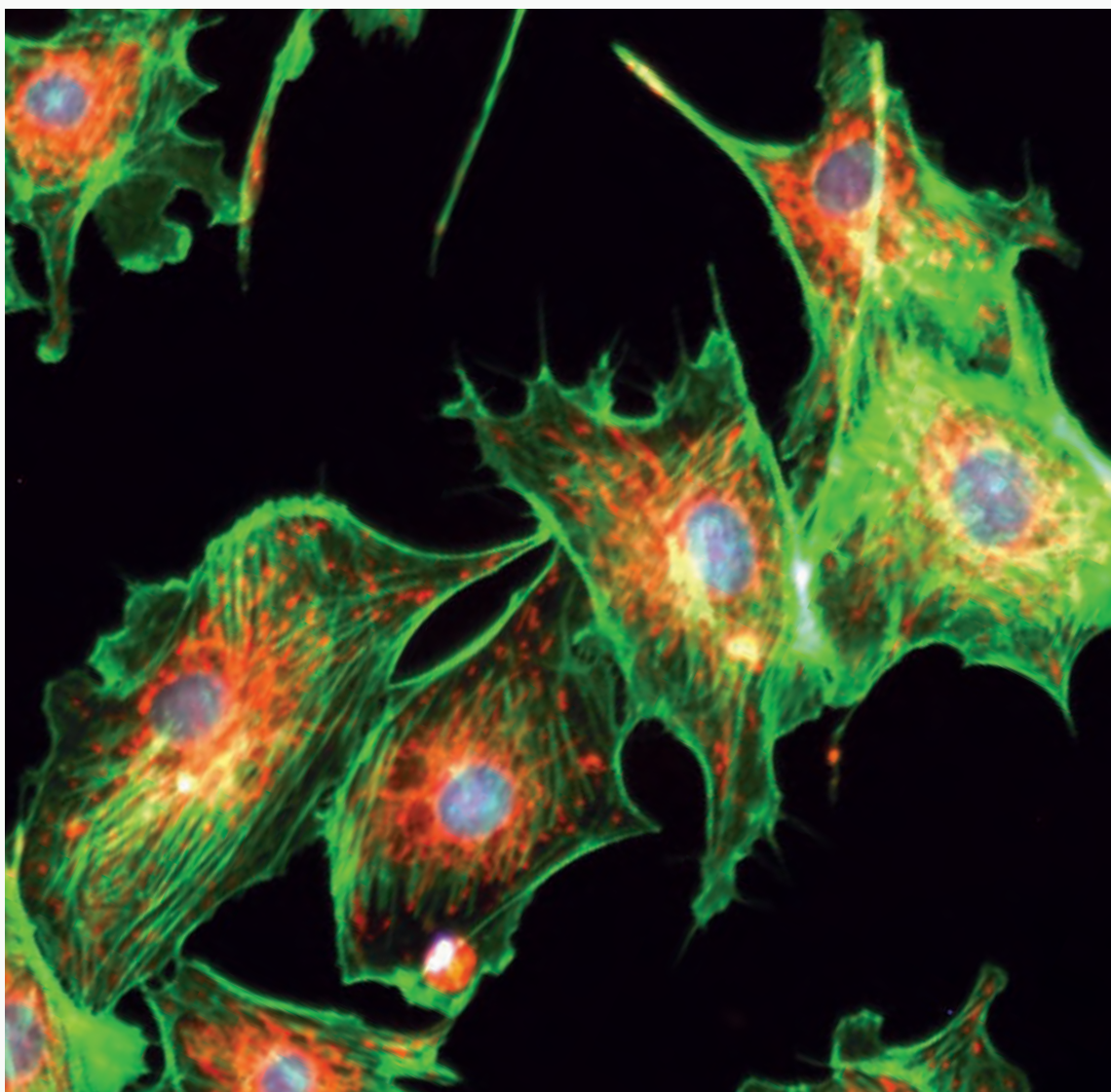
“What we’re doing right now is to focus on the places where the genetics is pretty strong—that’s our tactical strategy, to look in places where people haven’t looked, but to target diseases where we know heritability is fairly strong,” he says. “Alzheimer’s disease, Fragile X, schizophrenia, and autism are all diseases of the brain that show a lot more genetic influence than something like cancer, which is to a great degree environmental—the things you do and don’t do. With mental diseases, diseases of the brain, the genes play a bigger role.”

*“With mental diseases, diseases of the brain,  
the genes play a bigger role.”*

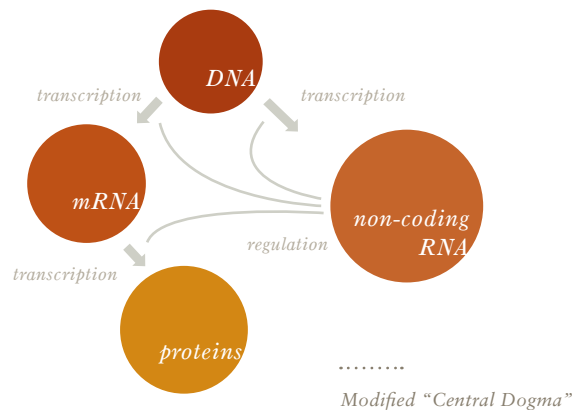
CLAES WAHLESTEDT, M.D., Ph.D.

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WATCHING THE DARK



Alzheimer's disease results in changes in cellular functioning in the brain.



### ALZHEIMER'S DISEASE PROGRESSION

In Alzheimer's research, there is a significant amount of evidence that the buildup of amyloid plaque—the tangled fibrils in the brain that characterize the disease—begins early, particularly the buildup of amyloid- $\beta$  1-42, the peptide believed to be the primary cause of Alzheimer's disease. While Wahlestedt's study supports this view, it also takes our understanding one step further, identifying one of the underlying mechanisms that plays a major role in that buildup. The study also provides a rare glimpse of therapeutic potential in what has been a fairly dismal science.

Wahlestedt's team showed that when BACE1-AS (pronounced *base*) is exposed to stress, it stabilizes BACE1 messenger RNA, increasing expression of BACE1, and with it, levels of amyloid- $\beta$  1-42.

Furthermore, the team used a synthetic small interfering RNA—which can inhibit gene expression—to successfully decrease BACE1-AS expression in animal models and reduce the production of amyloid plaque.

"Those animal model experiments support the validity of a siRNA approach, perhaps in humans as well," he says. "Recent technological breakthroughs suggest that systemic administration of modified siRNA, which crosses the blood-brain barrier, could easily target RNA transcripts there. Alternatively, proteins involved in BACE1-AS localization or turnover could also become targets for potential therapeutics."

While many unanswered questions remain,

Wahlestedt remains encouraged by the team's progress.

"Even if we don't have the entire solution yet," he says, "we have moved our understanding of it much further upstream."

### FRAGILE X QUESTIONS

That's also the case with the team's investigations of Fragile X syndrome, for which there are currently no therapeutic treatments.

Fragile X is linked to inactivation of FMR1 gene expression, a protein known as the Fragile X mental retardation protein, now considered to be critical for neuronal function. The FMR1 gene locus—a specific point on a chromosome—is not well mapped. Until Wahlestedt's 2008 study, it was thought that FMR1, which was discovered more than 16 years ago, was the only gene involved in the disorder.

But Wahlestedt and his colleagues hypothesized that unknown regulatory genes might be transcribed from the FMR1 locus. And, indeed, they found FMR4, which is not a conventional gene but rather a non-coding RNA transcript.

"FMR4 is a novel gene that is located in the same chromosomal neighborhood as FMR1, a well established cause of Fragile X," Wahlestedt says. "Like FMR1, FMR4 is silenced in Fragile X patients and up-regulated in FXTAS (fragile X-associated tremor/ataxia syndrome), a disease which resembles Parkinson's and Alzheimer's."



*“My interest is really a duality. It is basic science, but we try to push it towards some kind of treatment or diagnostic test.”*

CLAES WAHLESTEDT, M.D., Ph.D.

According to the study, FMR4 directly affects human cell proliferation *in vitro*—when silenced, it causes changes in the cell cycle and a rise in apoptosis or programmed cell death. Overexpression, on the other hand, leads to increased cell proliferation. The full meaning of this anti-apoptosis function is still unclear.

Both of Wahlestedt’s studies illuminate the mission of The Translational Research Institute at Scripps Florida, which is focused on translating basic research, such as the discovery of FMR4, into potential new therapeutics. The Translational Research Institute has a structure similar to a drug discovery company, and many of the researchers have pharmaceutical experience.

#### A DUAL INTEREST

It takes a certain mindset to use basic science to uncover potential drug candidates.

“My interest is really a duality,” he says. “It is basic science, but we try to push it towards some kind of treatment or diagnostic test. Most people who work on noncoding RNA don’t think about drugs. And then you have the other end, those drug discovery people in the industry who usually don’t get an opportunity to work extensively on basic science. My background gives me a little bit of both.”

Wahlestedt, 49, has been with Scripps Florida since 2005. Prior to that, he was the founding director of the Center for Genomics and Bioinformatics

at the Karolinska Institute in Stockholm, Sweden. He also spent a decade directing drug discovery and genomics efforts in the pharmaceutical industry.

His dual interest and background have made it natural for him to take the first step in commercializing some of his own findings. In August 2008, Wahlestedt announced the formation of CuRNA, a new company based on an advanced technology licensed from his work at The Scripps Research Institute’s Jupiter facilities.

“We have licensed a fairly broad patent with many different targets in major therapeutic areas that fall under the non-coding RNA umbrella including metabolic disease and cancer,” Wahlestedt says, “Depending on the specific nature of the RNA involved, they can either elevate or suppress gene expression. These things can be used in a number of important ways—to treat disease or as diagnostic markers or tools. All in all, they have some significant therapeutic as well as diagnostic potential.”

Wahlestedt’s work now seems to be perfectly balanced, straddling that most interesting point between the lamppost and the surrounding darkness, although in his case, the dark may have a slight advantage.

“We continue to work as always,” he says. “One answer generates 100 questions. But I do think we have provided ample proof of concept that the universe outside the lamppost is well worth looking at.”

ERIC SAUTER



*“We are who we are in large part because of what we have learned and what we remember.”*

MARK MAYFORD, Ph.D.



## Permanent Ghosts

MARK MAYFORD PINPOINTS THE STUFF OF MEMORY

Mark Mayford, Ph.D., associate professor in the Department of Cell Biology and a member of the Institute for Childhood and Neglected Diseases at The Scripps Research Institute, has always been fascinated by memory. His groundbreaking study published February 22, 2008, in the prestigious journal *Science*, carried that fascination into an entirely new realm, one that seems both familiar and more than a little strange.

Mayford has written about the nuances of such work himself, describing the ability to form memories as perhaps the most significant and distinctive feature of our cognitive life: “We are who we are in large part because of what we have learned and what we remember,” he says. It is, more or less, what makes us human. What Mayford has done is to dissect this fundamental humanness, burrowing into the molecular realm to investigate those events that are involved in learning and memory and in the process when molecules go astray and memories vanish.

Disruptions in learning and memory are part of a range of disorders that plague human beings at different stages of life, from childhood forms of mental retardation and adolescent psychiatric disorders such as schizophrenia to all-too-familiar diseases of aging like Alzheimer’s disease.

To varying degrees, these are all memory problems, which, for Mayford, means these are all molecular problems.

### A NEW LEVEL OF SPECIFICITY

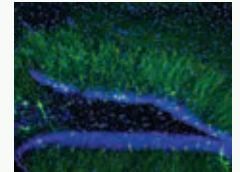
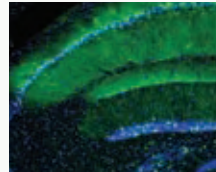
In his breakthrough study, Mayford and his colleagues pushed these molecular studies to a new level of specificity, identifying for the first time the precise synapses on neurons that are critical components of the learning process and the development of long-term memory, at least in mice.

The team showed that 24 hours after learning to fear a specific place, neurons in the brain’s memory hub, the hippocampus, demonstrated an increased ability to retain newly synthesized proteins called AMPA receptors. The surge in capture of the receptors appeared within hours of learning and was gone after a few days, but appeared to be critical for cementing the memory.

This was a key finding and added new weight to the idea that AMPA receptors strengthen memories by becoming part of the synapses, the gaps between the ends of nerve fibers that are traversed by nerve impulses passing from one neuron to another. These impulses travel to and from spines, parts of the neuron that protrude in branch-like projections and the site of most of the brain’s connections. →

#### Moving AMPA Receptors.

This image shows the hippocampus 24 hours after forming a new fear memory. The newly made AMPA receptors (green) are moving out from the cell bodies (blue) to participate in dendritic processes making connections.



The scientists found increased molecular trafficking to only one particular type of spine, called the mushroom spine. The other types (the thin and the stubby spines) showed no change. Mayford's study was the first to show a distinct difference in molecular signaling among various spine types.

The mushroom spines also figured prominently in the same neurons when the fear conditioning was reversed by repeatedly exposing the animals to the feared location in a benign way, a procedure called extinction learning. This indicated that the same neurons are activated when a fear is learned and when it is lost.

While there is still much to learn about the function of differently shaped spines, scientists do know their distribution is altered in various forms of retardation like Fragile X syndrome and Down syndrome. Mayford's research adds weight to the idea that different spine types may play distinct key roles in mental functioning.

#### MEMORIES ARE MADE OF THIS

Like a leaf floating on a current of water, neuronal activity follows a sensory stream. A beam of light falls on the retina, neurons in the eye react to the stimulus, and they connect with neurons in the brain. Our perception of that beam of light, and whether it represents a rainbow or a tree, occurs deep in our brain and depends on the precise flow and branching pattern of the sensory stream. Neurons fire at different rates, depending on just how many synaptic inputs they're receiving from up-

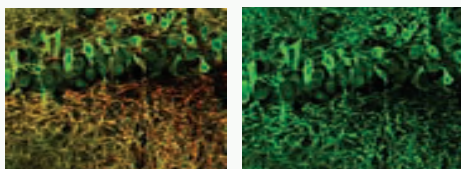
stream neurons; if the neuron receives enough synaptic signals, the neuron fires and the stream of information continues to flow down that branch. The varying strengths of these synaptic signals are the dams and levees that sculpt the flow of information throughout the brain.

It is in these molecular fire points that the process of memory begins and where Mayford has long parted company with one major theory of memory, which equates memory with the process called long-term potentiation (LTP).

As neurons fire and release neurotransmitters onto downstream cells, it is believed that LTP strengthens the synapses between the neurons by increasing the response of the receiving cell to the neurotransmitter. It's a phenomenon that is observable primarily in experimental environments and many scientists believe it is the mechanism for learning and memory. "It's what we call Hebbian," Mayford says, "a learning mechanism that occurs when the synapses between two cells grow stronger as they repeatedly fire at the same time." A short hand of this theory is cells that fire together, wire together.

For Mayford, and increasingly for other scientists, LTP has its limitations.

"There are data to support the role of LTP in memory, as well as data that complicate the notion that it is deeply involved," he says. "While LTP clearly has attractive features for a memory mechanism, it's just too simplistic to say there is a one-to-one correlation between LTP and long-term memory."



Mayford's research provides a novel framework for a number of molecules that he believes are essential for long-term memory. His biggest problem—the problem of all memory research—is putting what is known at the molecular level together with what is known at the circuit level to create a clear understanding of what's actually happening inside the brain.

#### DIVING INTO THE MYSTERY

Some of Mayford's approach to this mystery is based on his earlier work with sea slugs—*Aplysia californica*—a long-favored laboratory specimen because of its simple circuitry that's easy to study. These homely creatures captured Mayford's attention just long enough for one major paper on how the mollusk's synaptic connections are altered by the neurotransmitter serotonin.

Soon after, Mayford, a Midwesterner who did both his undergraduate and graduate work at the University of Wisconsin before moving to New York in 1997 for a postdoctoral fellowship at Columbia University, shifted his focus. Moving away from both sea slugs and, to a certain degree, LTP, he now concentrates on various molecules that he studies in mouse models. With that change, he has taken his own dive into the deep blue mystery of memory—what the novelist Cynthia Ozick once called “permanent ghosts.”

Mayford has shown that there are certain molecules important to the formation of memory—specific kinases, neuroreceptors, and transcription

factors. When these molecules get disrupted in the brain, memory gets destroyed.

To better understand how these molecules work, Mayford and his colleagues develop new strains of transgenic mice. The results of this year's *Science* study, for example, were made possible by a mouse model that enabled the scientists to monitor the trafficking and turnover of newly synthesized AMPA receptors produced at the time of learning.

“Because AMPA receptors had shown the ability to change trafficking patterns and move into synapses during long-term potentiation, there was ample reason to think it was important to the learning process,” Mayford said. “Consequently, we developed a mouse model that allowed us to monitor these new AMPA receptors visually with a green fluorescent stain as they traveled to the tagged synapses.”

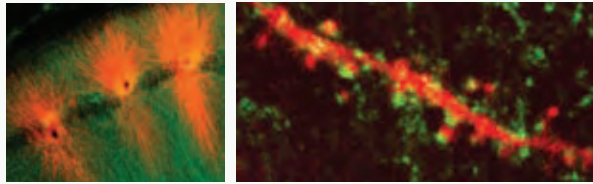
In the study, once new AMPA receptors were triggered deep in the neuron's nucleus, the researchers chemically suppressed further expression. This allowed time for the receptors to migrate to their appointed synapses. Hours later, green fluorescence revealed the fate of the specific AMPA receptors born in response to the learning—and new light was shed on the process of memory.

Much of Mayford's laboratory time since the study has been spent producing more mouse models.

“These models give us genetic control over brain circuits that make up specific memories,” he says, “so we can begin to study specific cells, how they connect, what happens when you change them

### Hitting the Target.

A red dye lights up the processes and dendritic spines of a single neuron. At high power (right panel), individual spines can be identified and it is clear that the AMPA receptors (green) travel evenly to every spine. Those spines receiving the new receptor may be the connections modified to form memories.



*“The brain activity patterns we study are memory.”*

MARK MAYFORD, Ph.D.

around, how they change with learning over time, and what happens when we silence them.”

#### WHAT YOU SEE IS WHAT YOU GET

In the Jim Carrey film, *Eternal Sunshine of the Spotless Mind*, the main character discovers that his former lover has had all memory of their affair erased by the aptly named Lacuna, Inc; lacunar amnesia is a missing piece of memory surrounding specific and isolated events. In the film, Carrey comes to fight for his memories.

Although Mayford doesn't often indulge in such fantasies, it is that clear that with this latest study he is touching on the very human question lurking at the outer edges of his research—if we can pinpoint where memories are made, will we be able to alter or remove them at will? This question, the basis of nearly every Philip K. Dick science fiction short story, not to mention the obsessive romanticism affecting artists from Proust to Adam Sandler—is something that Mayford thinks about from time to time.

Ironically, Mayford has seen the movie but has forgotten the finer details of the plot. Although he thinks you could actually target active neurons to erase a specific memory, he doesn't take the idea all that far.

For Mayford, what you see is very much what you get.

“The brain activity patterns we study are memory,” he says. “The brain is made up of a group of chemicals and our behavior is derived from those.”

What Mayford is ultimately interested in knowing is the exact nature of the molecular changes that underlie the formation of memory because that is how the normal brain works. And from there, he's interested in finding out the nature of all the things that go wrong in some illnesses—and, potentially, drug targets for therapeutic interventions in diseases such as schizophrenia.

“What is a hallucination?” he says. “It's probably just a bad pattern of neuronal activation. At a cursory level, we want to learn which neurons we need to study. And then we want to look at those neurons and how they change over time. Does memory involve changes in neuronal structure or is it something else? Why do some memories last a lifetime?”

That same sort of question is posed by characters in science fiction movies.

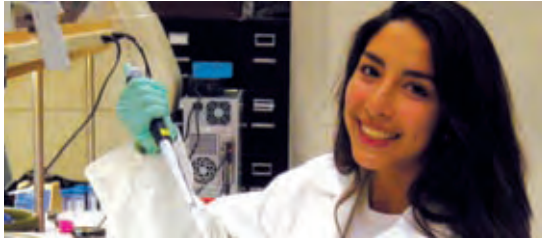
“That's what we're trying to do, at least in terms of mice,” he says. “It just hasn't reached the movie level yet.”

ERIC SAUTER

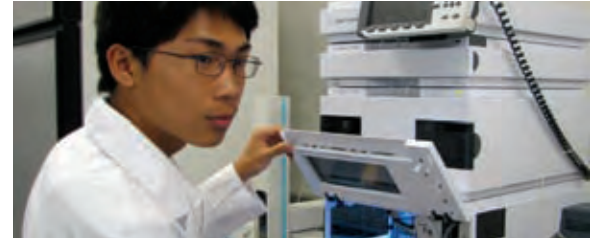
The background of the page is a light blue color with faint, handwritten notes and diagrams in a darker blue or green ink. The notes include the letters 'AT', 'K', 'A', and '279300'. There are also some diagrams, including one with a box and lines, and another with a vertical line and a horizontal line. The handwriting is somewhat messy and appears to be from a student or researcher.

## *Special Education Section*

**PAGE 30**, SCRIPPS RESEARCH SCIENTISTS, INTERNS SHARE ENTHUSIASM ABOUT SCIENCE; **PAGE 32**, SCRIPPS RESEARCH CELEBRATES EXCELLENCE IN EDUCATION AND RESEARCH; **PAGE 34**, ELEMENTS OF SUCCESS : EXCERPTS FROM ERNEST BEUTLER'S COMMENCEMENT ADDRESS; **PAGE 35**, IN MEMORIAM : ERNEST BEUTLER, M.D. (1928 - 2008); **PAGE 36**, THE IMPORTANCE OF HERITAGE : EXCERPTS FROM REMARKS BY CLAUDIA SKAGGS LUTTRELL



1989 - 2008



## Scripps Research Scientists, Interns Share Enthusiasm About Science

There were no worries about a boring summer vacation for Scripps Research Institute interns on both coasts. Instead, the summer found these individuals in the lab, helping to explore new territory in fields from cancer biology to Huntington's disease.

### Hands-On in the Lab

The Research Education Program in La Jolla, California, now in its 19th year, received some 10 applications from local high school students for every position available on the California campus. The 24 students chosen represented 13 schools in San Diego County. Three high school teachers also participated, with the goal of bringing a new perspective on science to their classrooms in the fall.

"The participants were outstanding," said Marisela Chevez, who directs the California program. "It was wonderful to see so much enthusiasm about science."

Before the high school interns arrived in Scripps California labs, they attended a series of spring enrichment tutorials, organized by Scripps Research Kellogg School of Science and Technology graduate students Dena Marrinucci and Kris Koudelka.

All interns also attended a week-long "boot camp," which covered basic lab procedures and other skills, including documentation, notebook entry, and lab safety. The seminar was held at Miramar College, in conjunction with interns at the Salk Institute for Biological Studies and the Burnham Institute for Medical Research, which shared the high school intern applicant pool.

By the time the interns reached their Scripps Research labs, they were ready to make the most of their hands-on experience. Each intern assisted in some way in a specific research project under the supervision of a mentor. Field trips and weekly lunchtime seminars supplemented the lab work. At the end of the program in August, participants presented their research projects to mentors, parents, and supporters in a day-long event.

### Career Plans in the Biomedical Sciences

For many student interns, the summer helped shape their future career plans. One of the 2008 interns, Kate Barker of Mission Hills High School, for example, comments, "I had an incredible time and learned so much. This experience has reinforced my desire to pursue a major in science and have a career in research."

As a follow up to the summer internships, California student interns also received some extra help with the next step—the college application process—at the institute in October. The workshop, now in its second year, pairs the former interns with graduate student mentors, who provide valuable feedback on the interns' proposed outlines and ideas for application essays.





Over the past several years, student interns—many of whom are the first in their family to attend college—have gone on to attend institutions including Harvard University, the California Institute of Technology, and the Massachusetts Institute of Technology.

Financial support for California internships was provided by the Biogen Idec Foundation, Diekman Fellowship, Ellen Browning Scripps Foundation, French/Masserini Charitable Trust (administered by Wells Fargo Bank), Hearst Foundation, Legler Benbough Foundation, Novartis Foundation, Shapiro Fellowship, and Valenzuela Charitable Trust. The week-long lab preparatory class was made possible by a partnership with the Life Science Summer Institute, sponsored by the San Diego Workforce Partnership and Biocom.

**Scripps Florida Program Blooms** The Scripps Florida campus offers its own summer internship program, which enables select Florida teachers and high school students to learn about contemporary issues in biomedical research and to work alongside world-class scientists and their staffs.

This year, the six-week internships attracted a pool of 90 applicants. Three teachers and 11 students were chosen to participate.

“This summer’s program was a great success,” said Deborah Leach-Scampavia, Scripps Florida’s education and outreach administrator. “Students and teachers got a close-up view of what goes into basic research in fields from cancer biology to bioinformatics.”

For many Florida interns, the impact of the experience has been long lasting. Out of the 27 former interns, seven have stayed on for part-time work in Scripps Florida labs. And, as in California, former Scripps Florida student interns have gone on to attend a variety of prestigious universities, including Harvard, Princeton, and Stanford.

New this fall, Florida teacher interns are not only sharing their new insights in their own classrooms, but are also sharing their knowledge by developing curriculum tools and portable science kits for science education and teacher professional development. These activities are being funded by a pilot project grant from the William R. Kenan, Jr. Charitable Trust, which also supports the larger Scripps Florida internship program.

In addition to the summer internships, Scripps Florida’s outreach programs include: a Science Saturday course designed to show high school students about biotechnology tools through a hands-on DNA forensics exercise; an Introduction to Science lecture and exercise designed to teach middle school students about our world; and a Biotechnology Tour providing an up-close view of Scripps Florida biomedical technologies.

In California, additional outreach programs include: the Summer Internship Program in Immunology for Undergraduates, sponsored by the Scripps Research Department of Immunology and Genentech, for a dozen undergraduates from across the country; MySci, a half-day science festival for San Diego high school students; and the Science Partnership Scholars Program, a five-week program sponsored by the Arthur Vining Davis Foundations for high school and middle school teachers who want to enhance their science curriculum.

## Scripps Research Celebrates Excellence in Education and Research

On Friday, May 16, 2008, The Scripps Research Institute celebrated its commitment to excellence in education and research with its 16th commencement, which graduated 28 Ph.D. candidates and recognized Scripps Research trustee Claudia S. Luttrell with an honorary degree. Delivering an inspiring keynote address was the late Ernest Beutler, a distinguished scientist and long-time Scripps Research faculty member.

The official ceremonies began with a winding march across the oceanside campus. Led by Scripps Research President Richard A. Lerner, M.D., the regal procession included not only Kellogg School of Science and Technology deans, the honorary degree recipient, faculty advisors, and graduating students, but also fellow Kellogg School students and faculty members.

Welcoming the winding procession in the Neurosciences Institute auditorium were enthusiastic friends, family, and well-wishers of the graduating students.

### A Powerful Mission

The 28 Ph.D. students in this year's graduating class represent fields from organic chemistry to molecular biology, and interests in topics from malaria to HIV.

A Ph.D. degree from the Kellogg School of Science and Technology takes an average of five years, in which the candidate attends classes, completes lab rotations, and writes a dissertation that offers an original contribution to the field. The institute's first commencement in 1993 graduated a single student. Since then, the program has grown rapidly in both size and reputation.

The Kellogg School can now boast of more than 300 accomplished alumni, including the Class of '08. Three of these alumni—two from this year's graduating class—conducted studies on the Scripps Florida campus, which accepted its first transfer students in 2005 and began accepting entering students in 2006.

The school's vigor is confirmed by stellar rankings from various organizations, including *U.S. News & World Report*, which continues to rank the Kellogg School among the top ten programs in both graduate biology and chemistry, based on the results of a survey sent to department heads and directors of graduate studies programs at universities throughout the country. An index of faculty productivity published in *The Chronicle of Higher Education* ranks the Kellogg School as best in the nation in biophysics, as well as second in immunology and seventh in biochemistry.

The stipends and tuitions of students of the Kellogg School are supported by generous donations from individuals, foundations, and corporations. New this year is the Leadership Fellows Fund, created by a three-year pledge from members of the Scripps Research Board of Trustees. The fund is currently supporting 15 first-year students.

*In the commencement ceremonies, each graduating student was honored individually, with Ph.D. advisors speaking about each graduate's array of scientific and personal accomplishments.*



**Looking Ahead** During the 2008 commencement ceremony, Beutler shared some words of advice with the graduating students on the keys to a successful career in science. (See excerpts, page 34.) After Beutler concluded his remarks, congratulating the students and their families, each student was honored individually. Ph.D. advisors stepped up to the stage one by one to speak about each graduate's array of scientific and personal accomplishments. It was a talented crowd.

Members of the Scripps Research Class of '08 will work in both academia and industry, including at the University of Chicago, Northwestern University, Burnham Institute, La Jolla Institute of Allergy & Immunology, and Scripps Research, as well as Pfizer, Celldex Therapeutics, Genomics Institute of the Novartis Research Foundation, Exelixis, and Johnson & Johnson.

Also recognized was *honoris causa* degree recipient Claudia Skaggs Luttrell. Luttrell spoke briefly, paying tribute to her father, Sam Skaggs, and reiterating her commitment to continuing his legacy and vision. (See excerpts, page 36.)

When Ph.D. degrees were officially conferred on the candidates and honorary degree recipient, the audience burst into thunderous applause.

## *Office Supports Junior Scientists*

How satisfied are postdoctoral fellows with their experience at The Scripps Research Institute? That was one of the underlying questions a recent survey conducted by the Office of Career and Postdoctoral Services set out to answer.

"Overall, the results from the survey are positive," said Ryan Wheeler, manager of the Office of Career and Postdoctoral Services. "Postdocs are largely satisfied with their research training experiences at the institute, and a strong majority would recommend Scripps Research to peers. Postdocs are particularly satisfied with the research environment and scientific expertise of their advisors."

Today's scientists typically spend two to five years after receiving their doctoral degree as a postdoctoral fellow, a.k.a. research associate, establishing

their ability to run a successful independent research program within another investigator's lab. This scientific apprenticeship usually serves as a stepping stone to career positions in academia or industry. The survey was conducted as part of the institute's reaccreditation process, which encompasses the institute as a whole, not only the graduate program.

Over the past five years, Scripps Research launched and expanded a series of initiatives to enhance the postdoctoral experience at the institute.

These included the establishment of an office dedicated to supporting Scripps Research postdocs and providing help with career transitions for both postdocs and graduate students. Today, the office hosts career seminars and sponsors a job board, among other activities.

*“Your greatest enemies are  
dogma and consensus.”*

ERNEST BEUTLER, M.D.

## Elements of Success:

EXCERPTS FROM ERNEST BEUTLER'S COMMENCEMENT ADDRESS

A few months before his death this year, Ernest Beutler—an eminent scientist who published more than 1,000 scientific papers, wrote more than 10 books, and chaired the Scripps Research Department of Molecular and Experimental Medicine for more than 30 years—addressed the graduating students and others in the auditorium, speaking to the joys of a career in science and keys to success.

Today you are receiving the academic degree that opens a door to what I truly believe is the most gratifying career upon which a person can embark. Society will provide you with the means of unraveling the secrets of nature, a wonderful and exciting challenge... For those whose enthusiasm, hard work, and good minds allow them to succeed, the gratification can be enormous. It is a career in which you are held in high regard by others for your accomplishments, in which you have an opportunity to work with talented and congenial colleagues, in which, through your efforts, you can add to the wealth of our society...

Lest you believe that the Nirvana that I have outlined is a certainty for all of you, let me qualify what I have said. Unfortunately, it doesn't describe what fate has in store for every budding scientist, but certainly for some, and very possibly for many of you. There is no magic formula that will ensure success, but there are a few ingredients that I regard to be very important. There is no substitute for hard work and a supportive family. A successful career in science demands scrupulous honesty and self-criticism... [I cannot emphasize too much how important it is to build a strong relation of mutual respect not only with your colleagues but also with your subordinates. You will build a team and it will be your responsibility to both guide and inspire them...]

What else is required? I would place the choice of a research topic near the top of the list. If 10 or 20 years from now you are elaborating on the work that you performed as a graduate student, your likelihood of success is not very high. On the other hand, if you have tackled 10 or 15 disparate projects during that time, the chances are that your career in science will not be fully gratifying. One must reach a compromise between being stuck in a rut, on the one hand, and sampling multiple projects as a humming-

bird samples flowers... I believe that the greatest error that young scientists make in choosing their first independent research projects is that they tend to run with the crowd. Today this might mean that they are compiling expression profiles of cancer cells. Or they are trying to show the roles of reactive oxygen species in aging, cancer, or what have you. Or perhaps they are trying to modify a cocktail of growth factors to improve slightly the maintenance of stem cells in culture. These are not bold initiatives. They are what thousands of others are doing, and you need to be very lucky, indeed, to have your work stand out.

The tendency to merely elaborate on what many others are doing arises, at least in part, from the almost universal misconception that our understanding of nature is profound, that most or all of the basic concepts have already been discovered, and that success in science consists of filling in the blanks with large teams of coworkers. Nearly every young scientist with whom I have had discussion about career bemoans the fact that the easy stuff has all been done, and now you must have a big team and a lot of money to make a contribution. I stand here to tell you that much of what your teachers believe and have taught you is wrong—wrong in part and sometimes in whole. One hundred years from now your scientific progeny will be laughing at our naïve and incomplete understanding of nature at the beginning of the 21st century. When I started in science we thought we knew a lot: DNA to RNA to protein. One gene, one protein. It had all been worked out. But no one had dreamed of introns, RNA editing, microRNA, or epigenetic imprinting. There is just as much waiting to be discovered in the years that lie ahead, and you should strive to make some of these totally unanticipated, fundamental discoveries. Your greatest enemies are dogma and consensus.



*In Memoriam:*  
Ernest Beutler, M.D. (1928 – 2008)

Ernest Beutler, M.D., a pioneering scientist who chaired the Scripps Research Institute's Department of Molecular and Experimental Medicine for more than three decades, died on October 5. He was 80.

"His passing is a great loss to science, to the institute, and to all who knew and worked with him over his long, brilliant career," says Scripps Research President Richard A. Lerner, M.D.

Ernest Beutler made important scientific contributions both in basic science and clinical medicine. He independently originated the X-inactivation hypothesis in 1961; played a major role in the discovery of G6PD deficiency, the most common clinically significant enzyme deficiency; developed a screening test for galactosemia; and was instrumental in developing diagnosis and treatment of Gaucher disease, cloning the gene mutations which cause this disorder. He created highly successful bone marrow transplantation programs and showed that the usual practice of transfusing platelets whenever the count fell to less than 20,000 was unnecessary and injurious to patients. At Scripps Research, with Dennis Carson, he developed 2-Chlorodeoxyadenosine, now a major treatment of leukemia and of multiple sclerosis. One of his more recent achievements was to show that the clinical penetrance of hemochromatosis is low and that this iron storage disease, far from being the most common disease of Europeans as was often thought, is actually quite rare.

Beutler was born in 1928 in Berlin, leaving Germany in 1935 with his family after Adolf Hitler's rise to power. The family resettled in Milwaukee, Wisconsin.

Beutler attended the University of Chicago, where he received both undergraduate and medical degrees. He remained there on the staff and faculty until 1959, at which time he was recruited to Southern California's City of Hope, where he established and served as chair of its Department of Medicine. In 1978, he joined Scripps Clinic and Research Foundation, precursor of The Scripps Research Institute, to chair what is now the Department of Molecular and Experimental Medicine. A physician as well as a scientist, he was also head of the Division of Hematology and Oncology at the Scripps Clinic for many years. Beutler's scientific leadership was recognized by numerous honors.

"Ernie was a truly extraordinary man who led an exceptional life, full of kindness, wisdom, strength, and knowledge," said Lerner. "We should be most thankful that he crossed our path and stayed with us for so long."

*"His passing is a great loss to science, to the  
institute, and to all who knew and worked with  
him over his long, brilliant career."*

RICHARD A. LERNER, M.D.



## The Importance of Heritage:

EXCERPTS FROM REMARKS BY CLAUDIA SKAGGS LUTTRELL

Claudia Skaggs Luttrell was awarded an honorary degree at the May 2008 commencement ceremonies at The Scripps Research Institute in recognition of her achievements, which include promoting scientific collaboration in her capacity as a member of the Scripps Research Board of Trustees, president of the Skaggs Institute for Research at Scripps Research, and chair of the Skaggs Oxford Scholarship Program, a joint academic training program at Scripps Research and Oxford University. Here are remarks she shared with the audience at that time.

It is really a distinct pleasure and honor to stand before you and accept an honorary degree from The Scripps Research Institute, which is world-renowned for biomedical research that is undertaken here by remarkable faculty that include Nobel laureates, members of the National Academy of Sciences, and fellows of several prestigious organizations. I am particularly proud to be associated with one of the country's largest private nonprofit research organizations that is at the forefront of basic medical research.

All things of real value, including academic degrees, have a heritage that is important to understand and appreciate. This is certainly true for those of you who are graduating today. You have not only earned a degree from a prestigious institution, but you have also garnered an academic heritage that will be especially important as you develop your careers as independent researchers.

Likewise, my honorary degree is linked with the heritage that I attribute to my father, Sam Skaggs, who was one of the giants of corporate America. The list of my father's accomplishments is extensive and so is his record of philanthropy. He was chairman and chief executive officer of Skaggs Companies, which later became American Stores Company.

My grandfather originally started Skaggs in 1940. Dad assumed the presidency of Skaggs, then an 11-store chain, with my grandfather's passing in 1950. Dad had just turned 26. In 1965, he took the business public on the New York Stock Exchange with 65 drug stores and sales of \$89 million. Although there were many successful mergers and acquisitions during Dad's reign, he will forever be known as the creator of the combination store, for

it was my father who pioneered the first successful combination food and drug store, literally changing the way America shopped.

Before his retirement in 1995, Dad had transformed the company into the second largest food company worldwide, with more than 1700 stores in 26 states and annual revenues of \$22.2 billion. If you ask Dad what he would have done differently if his father had not passed away at such a young age, he will simply tell you he wanted to be a pharmacist.

He shares your passion towards biomedical science and research, and the pursuit of medical and scientific excellence. He is a quiet philanthropist with a deep concern for humanity. He also loves this institute. Twelve years ago, he invested in the future of TSRI with a donation of \$100 million.

My father's philosophy is grounded in a strong belief that basic biomedical science should translate into new medicines to treat disease, new diagnostic tests, and new methods to prevent disease. This remarkable institute fulfills this philosophy by training the next generation of scientists, while at the same time contributing to the scientific knowledge base that, in turn, leads to new discoveries for drug targets and new biological markers for disease.

I am very well aware that I am the next generation who has the responsibility to carry on my father's legacy and vision into the future. I am honored to accept this degree as a reflection of my belief in the importance of education and medical research and the results from these endeavors for the betterment of humankind. I am confident that, teamed together, we can and will continue to achieve biomedical milestones that further advance local healthcare and my father's vision.

# Scripps Research Financial Highlights

FISCAL YEARS ENDING SEPTEMBER 30

## Sponsored Programs

(millions)

06		322.6
07		308.5
08		523.9

## Total Assets

(millions)

06		330.4	226.2	75.7	632.3
07		379.8	292.0	96.1	767.9
08		325.9	378.8	114.6	819.3

■ Investments  
 ■ Property  
 ■ Other

## Net Assets

(millions)

06		483.1
07		524.6
08		662.5

## Asset/Debt Ratio

(millions)

06		(632.3/58.9)	10.7
07		(767.9/57.2)	13.4
08		(819.3/55.3)	14.8

## Net Income

(millions)

06		63.3
07		41.5
08		137.9

# THE LEGACY OF THE SKAGGS FAMILY

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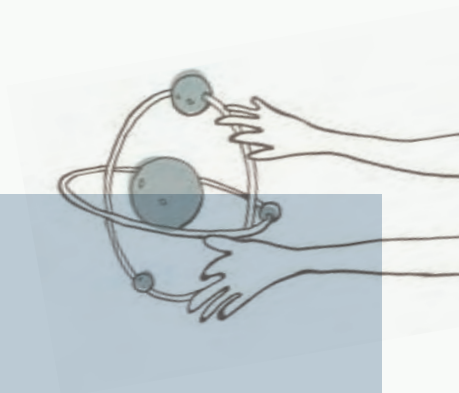
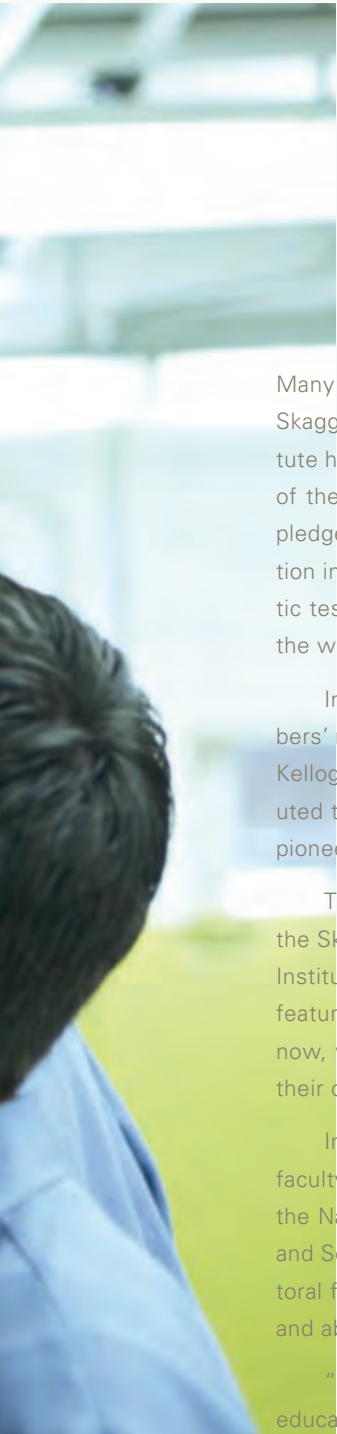
THE LEGACY OF THE SKAGGS FAMILY



*“The most important products  
of the Skaggs Institute are the  
people that are educated here.”*

JULIUS REBEK, Ph.D.





## *The Next Generation: The Skaggs Institute Shapes Future Scientific Leaders*

Many significant accomplishments have been made possible by the generosity of the Skaggs family. The centerpiece of the family's efforts at The Scripps Research Institute has been the Skaggs Institute for Chemical Biology, established in 1996 with one of the largest gifts ever received by a biomedical research institute—a \$100 million pledge to Scripps Research by L.S. “Sam” and Aline Skaggs. Excellence and innovation in biomedical science at the Skaggs Institute has led to new medicines, diagnostic tests, and methods to combat disease and promote human health. But that's not the whole story.

In addition, excellence in training at the Skaggs Institute—through faculty members' mentoring of postdoctoral fellows and their participation in the Scripps Research Kellogg School of Science and Technology and other training programs—has contributed to the emergence of a new generation of scientific leaders who are conducting pioneering research at the intersection of chemistry and biology.

This is the second in a series of articles highlighting the tremendous impact of the Skaggs family. While the first article focused on some of the projects that Skaggs Institute investigators have brought to the point of clinical development, this piece features some of the people who trained at the Skaggs Institute—where they are now, what their time at the Skaggs Institute meant to them, and how it has shaped their careers so far.

In fewer than a dozen years, the Skaggs Institute of Chemical Biology and its faculty—including three Nobel Prize winners, four Wolf Prize winners, 12 members of the National Academy of Sciences, and 13 fellows of the American Academy of Arts and Sciences—have played a key role in training more than 200 doctoral and postdoctoral fellows, who have gone on to high-powered positions in both the United States and abroad and whose influence is already being felt in their fields.

“The most important products of the Skaggs Institute are the people that are educated here,” said Julius Rebek, Ph.D., who directs the Skaggs Institute. “It has an enviable record of producing new faculty members worldwide. Just from my own research group, there are now professors at prestigious institutions in the United States such as Columbia, Duke, and the University of California, San Diego, as well as internationally in Germany, Switzerland, Austria, Italy, Spain, England, and Japan. All of these young professors got their training support with Skaggs Fellowships here at Scripps Research, so the impact of the Skaggs family support is international.”



ALAN SAGHATELIAN,  
Ph.D.

## ❖ COMPLEMENTING CHEMICAL SKILLS WITH BIOLOGY

One of the individuals whose scientific career has been shaped by the Skaggs Institute is Alan Saghatelian, Ph.D., now an assistant professor in the Department of Chemistry and Chemical Biology at Harvard University. Saghatelian received his doctorate with Skaggs investigator and Scripps Research Professor Reza Ghadiri, Ph.D., and completed his postdoctoral work in the laboratory of Skaggs investigator Benjamin Cravatt, Ph.D., chair of the Scripps Research Department of Chemical Physiology.

Well-positioned to make significant and potentially transformative discoveries, Saghatelian recently received a New Innovator Award from the National Institutes of Health. He is working to better define molecular pathways that underlie disease. His work focuses on a technique called discovery metabolite profiling (DMP), which examines the actions of specific enzymes in living cells, focusing not on the enzymes themselves, but on the substrates upon which they act. He plans to examine the function of enzymes associated with diseases such as diabetes, cancer, and schizophrenia.

“By targeting enzymes of biomedical interest, we hope to demonstrate the value of DMP in translational research through the identification of new drug targets and biological mechanisms,” Saghatelian says. “In the coming years, the applicability of DMP, as with any method that interfaces with genetics, should grow tremendously.”

Saghatelian looks on his training at the Skaggs Institute at Scripps Research as pivotal to his career.

“Coming into Scripps Research from UCLA, I had a strong chemical background,” he says. “At the Skaggs Institute, I complemented my chemical skills by receiving a thorough knowledge of biology in an intensely research-focused environment. I have taken the techniques I learned at Scripps Research and applied them at Harvard. In fact, the NIH Award I received at Harvard is based on the work I did at Scripps Research.”

Saghatelian is one of the young stars in the field of chemical biology and is one of the few people brave enough to tackle the characterization of the metabolome in health and disease—courage that likely will be rewarded by new insights into human maladies.

*“At the Skaggs Institute, I complemented my chemical skills by receiving a thorough knowledge of biology in an intensely research-focused environment.”*

ALAN SAGHATELIAN, Ph.D.



JIANMIN GAO, Ph.D.  
(top)

PER HAMMARSTROM,  
Ph.D.  
(bottom)

*“I benefited tremendously from the truly interdisciplinary nature of the Skaggs Institute.”*

JIANMIN GAO, Ph.D.

## EXPERTS IN ALMOST EVERY SUBFIELD

Jianmin Gao, Ph.D., now an assistant professor of chemistry at Boston College, served as a postdoctoral fellow at the Skaggs Institute under Jeffery Kelly, Ph.D., chair of the Department of Molecular and Experimental Medicine and Lita Annenberg Hazen Professor of Chemistry. Kelly is also chair of the Board of Trustees of the Skaggs Institute for Research, one of the Skaggs family’s major mechanisms for its philanthropy.

“I benefited tremendously from the truly interdisciplinary nature of the Skaggs Institute,” said Gao. “The institute houses experts in almost every subfield of science, and the faculty are happy to help and eager to

exchange ideas, which greatly broadens the horizon of scientific problems one dares to tackle.”

At Boston College, Gao is working on protein folding and aggregation, specifically on the folding mechanisms of beta-structured membrane proteins, which play vital roles in cancer biology. Gao strives to use chemical tools to bring a fresh look at biological problems.

Understanding the chemistry and biology of membrane protein folding is a substantial challenge, and Gao’s approach is likely to yield considerable insight into these proteins, which malfunction in numerous human diseases.

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## AN APPETITE FOR CROSSING DISCIPLINES

Now a professor of protein chemistry at Linköping University in Sweden, Per Hammarstrom, Ph.D., was also a postdoctoral fellow for Kelly at the Skaggs Institute.

“The Skaggs Institute is spearheading the field of chemical biology,” said Hammarstrom. “The interdisciplinary working environment where chemistry was the center of attention really fostered my appetite in continuing in the same spirit. I had a marvelous time at the institute.”

Hammarstrom is now working on diseases associated with the accumulation of misfolded proteins, including Alzheimer’s disease and prion diseases. He is searching in the dark corners of conformational path-

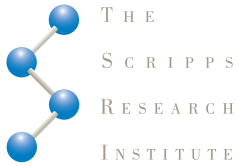
ways populated by certain proteins that ultimately cause neurodegenerative diseases. He attacks these issues by studying a selection of mutated proteins and applies both new biophysical methods and transgenic model systems to identify common species formed during protein misfolding.

Hammarstrom has received several young investigator awards, which have made it possible for him to establish a competitive research group. His pioneering efforts in the synthesis of polymers that detect aggregated proteins are likely to provide new insights into diagnosing and treating diseases, including Alzheimer’s and Parkinson’s.

THE LEGACY OF THE SKAGGS FAMILY



You, too, can help support breakthroughs like these. To learn more about the Skaggs Institute and other initiatives at Scripps Research, or to make a donation, call the Office of Philanthropy at (858) 784-2915 (California) or (561) 656-6400 (Florida). Also, see [www.scripps.edu/philanthropy](http://www.scripps.edu/philanthropy).



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