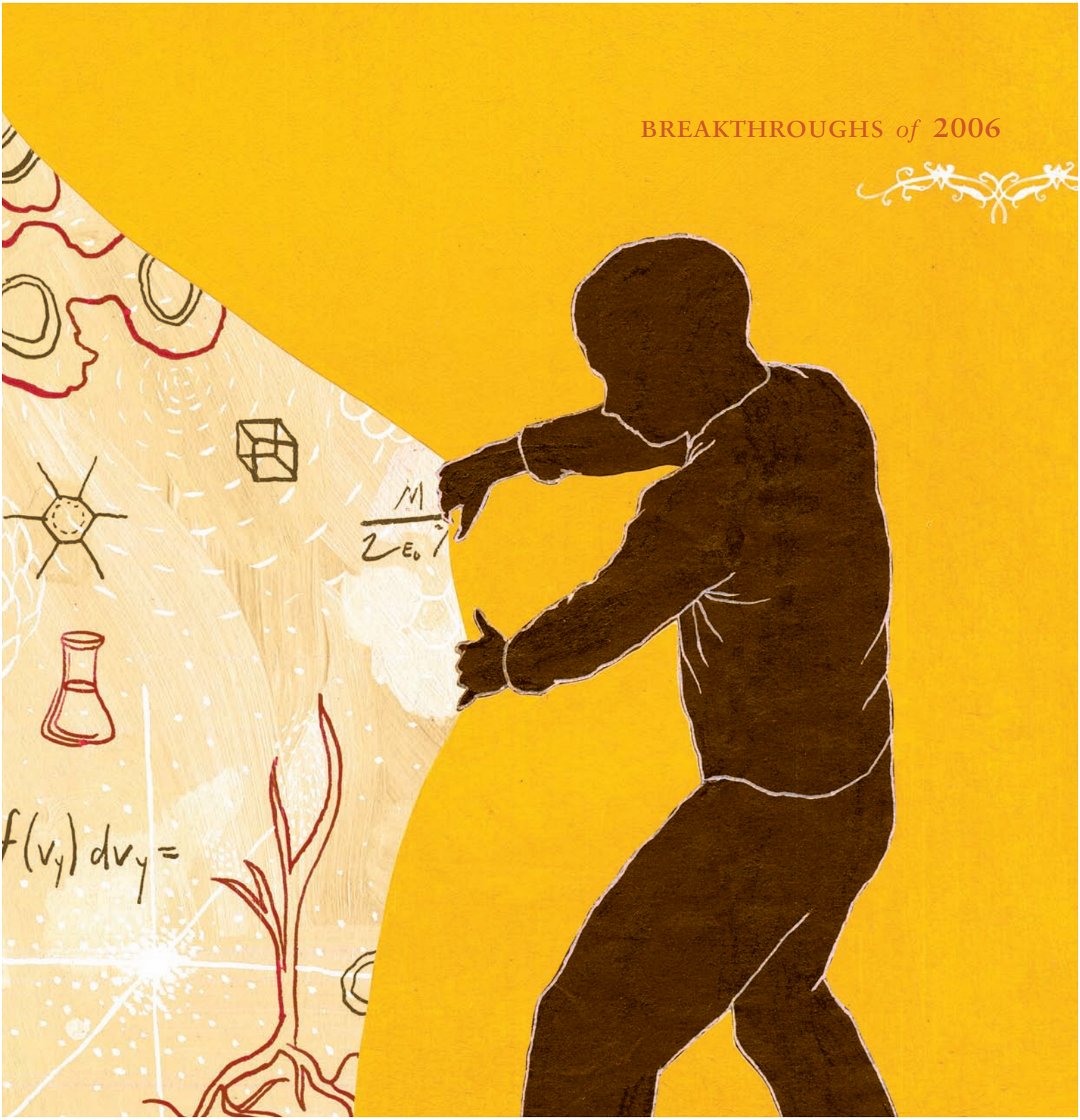
WINTER 2006/07

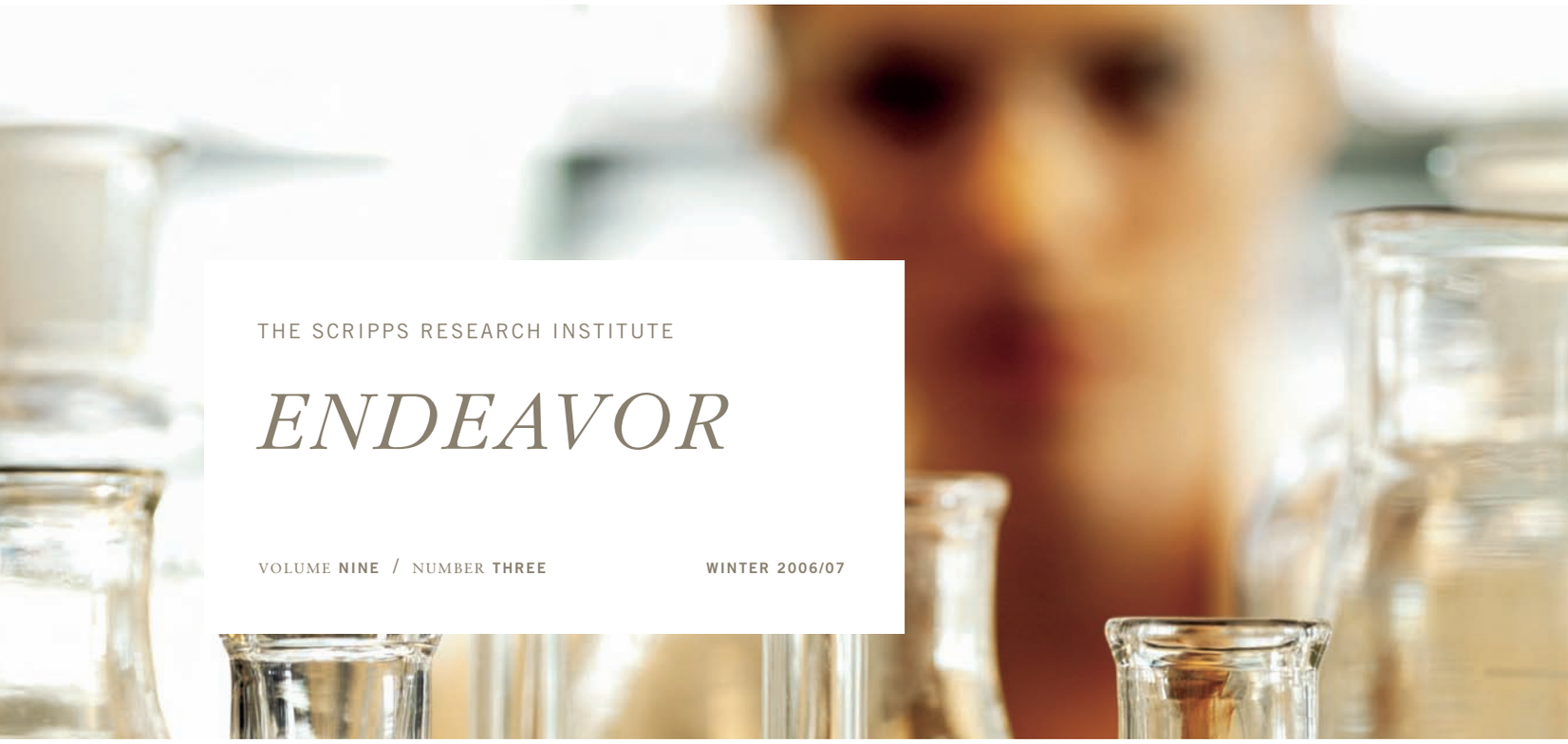
VOLUME NINE / NUMBER THREE

THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR

BREAKTHROUGHS *of* 2006



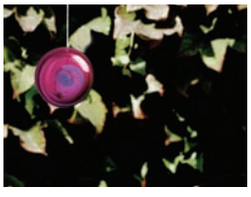


THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR

VOLUME **NINE** / NUMBER **THREE** **WINTER 2006/07**

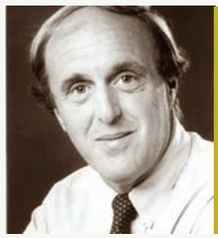
FEATURES:



ALSO:

ENDEAVOR IS A PUBLICATION OF
THE SCRIPPS RESEARCH INSTITUTE

This issue of *Endeavor* features some of the many scientific breakthroughs of 2006 from investigators at The Scripps Research Institute.



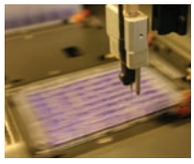
Richard A. Lerner, M.D.
President

Year in Review : 2006

PRESIDENT'S LETTER

One of the pleasures of being associated with The Scripps Research Institute is that we so often have good news to report. So it is this year, when we can share progress on our site in Florida, new contributions of our faculty, staff, and trustees in both Florida and California, and groundbreaking research in our understanding of health and disease. →

New Scripps Research facilities and alliances advanced in 2006.



FLORIDA ADVANCES

With the Palm Beach County commissioners' selection in February of a new site for Scripps Florida—on the Florida Atlantic University (FAU) north campus in Jupiter—we have moved forward with plans for a permanent facility. Scheduled to open in 2009, the facility will be a 350,000 square-foot, world-class biomedical research operation focusing on basic biomedical science, drug discovery, and technology development.

In the meantime, Scripps Florida opened a second temporary building this fall on the FAU site. The structure will provide 33,000 square feet of space to continue growing our faculty and staff while the permanent campus is under construction.

The state-of-the-art screening technologies at Scripps Florida have begun to make contributions to science, including published papers this year. The system, which relies on automated robots to analyze a large number of compounds at once, is available to Scripps Research faculty on both coasts. In January, the Access to Technologies Program also opened the system to scientists from universities and research institutions throughout Florida, enhancing our other collaborations in the state.

The State of Florida awarded its first research grant to one of our faculty members this year. Awarded on the basis of scientific merit, the Florida Department of Health's James & Esther King Biomedical Research grant will provide support for Layton Smith, Scripps Florida associate director of pharmacology, who is conducting research in the field of metabolism.

In another Florida development, this year we welcomed our first entering classman to our graduate program in Jupiter, where he joins several students who transferred from other institutions. A new two-way, web-based conferencing technology is enabling Florida students to participate in California lectures in real time, as well as open future Florida classes to interested California students.

NEW RESEARCH ALLIANCES

In 2006, we forged a number of new alliances, which will advance science at the institute in the years ahead.

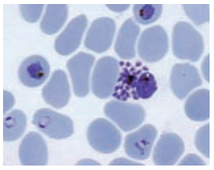
In February, we announced a collaborative initiative with IBM, called "Project Check-mate," that will conduct research on pandemic viruses to develop ways to anticipate, manage, and contain infectious diseases. Check-mate capitalizes on Scripps Research's world-class research in biochemical modeling and drug discovery and IBM's expertise in computational biology bio-patterning and supercomputing. The joint research team will harness both IBM's Blue Gene supercomputer and Scripps Florida's screening technology.

In March, we joined forces with three preeminent San Diego research institutions—The Burnham Institute for Medical Research, the Salk Institute for Biological Studies, and the University of California, San Diego (UCSD)—to establish an independent, non-profit consortium dedicated to stem cell research. The alliance, called the San Diego Consortium for Regenerative Medicine, will explore the tremendous therapeutic potential of stem cells to repair and replace damaged tissue.

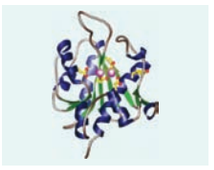
In April, we became part of Microsoft's new BioIT Alliance, a cross-industry group working to integrate science and technology to speed the pace of drug discovery and development. The alliance's first project, Collaborative Molecular Environment, strives to make research more efficient through a data management solution targeting common technology problems faced in the life sciences.

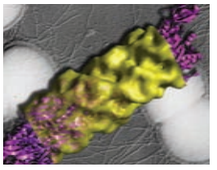
In May, a new robotic crystallization facility opened on the California campus, thanks to support from the Joint Center for Structural Genomics (funded through the NIH's Protein Structure Initiative) and global nonprofit group International AIDS Vaccine Initiative. One of the largest machines of its kind, the integrated robotics system will enhance scientists' ability to solve molecular structures, increasing our understanding of basic biology and strategies for combating a variety of diseases.

2006



A study found hundreds of novel genes that help the malaria parasite avoid destruction.





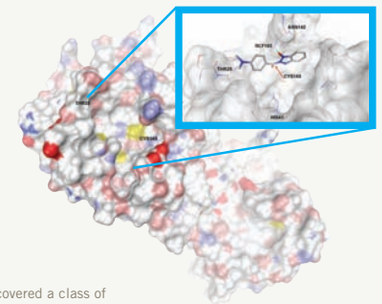
Researchers solved the structure of WRN, which protects humans from premature aging and cancer. They also solved the bacterial gc type iv pilus filament, which enables antibiotic-resistant bacteria to cause persistent and recurrent gonorrhea infections.

GROUNDBREAKING RESEARCH

Scripps Research continues to make significant strides and contributions to science.

The institute's science stands at the forefront of basic biomedical research, a vital endeavor that seeks to comprehend the most fundamental processes of life.

In addition to the research featured in this issue of *Endeavor*—on an anti-obesity vaccine, reactivation of the gene responsible for Friedreich's ataxia, heart damage from prion disease, and the threat of the avian flu virus—in 2006 Scripps Research scientists made many significant contributions. To name just a few key studies:



Scientists discovered a class of compounds that block the SARS virus from replicating.

+ Scientists demonstrated an innovative combination of immunotherapy and small molecule drug design for producing anti-cancer targeting antibodies. One study, led by Professor Carlos Barbas III, highlighted the potential of such an approach against melanoma. Another study, led by Associate Professor Subhash Sinha and myself, developed a compound against metastatic breast cancer.

+ Professor Chi-Huey Wong and colleagues discovered a class of compounds that block the SARS virus from replicating, a finding that may open the door to new drug targets against the deadly disease.

+ Professor Dale Boger and Kellogg School Ph.D. candidate Brendan Crowley re-engineered a well-known antibiotic to insure its effectiveness against sensitive as well as resistant enterococci, a common strain of bacteria responsible for wide-spread hospital infections.

+ Professor John Tainer and colleagues determined the crystal structure and molecular mechanisms of a key part of WRN, a protein that protects humans from premature aging and cancer. They also uncovered the structural chemistry behind the bacterial GC Type IV pilus filament, which plays an essential role in allowing antibiotic-resistant strains of *N. gonorrhoeae* to escape the immune system and cause persistent and recurrent gonorrhea infections.

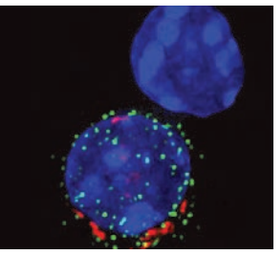
+ Professor Hugh Rosen and colleagues developed a chemical tool that allows manipulation of the passage of substances through the barriers between blood and organ tissues, findings that have therapeutic implications for organ transplants, autoimmune disease, multiple sclerosis, and adult respiratory distress syndrome.

+ Immunology Department Chair Richard Ulevitch and colleagues uncovered a new and potentially important function for the protein Nod1, inhibiting the growth of estrogen sensitive human breast cancer cells.

+ Associate Professor Elizabeth Winzeler and colleagues discovered hundreds of novel genes that may help the malaria parasite evade destruction by the human immune system and anti-malarial drugs. The findings could lead to the development of new therapies or vaccines for the deadly disease.

OTHER NOTEWORTHY DEVELOPMENTS

MNew agreements with Novartis and the Genomics Institute of the Novartis Research Foundation (GNF) will provide approximately $50 million over the next five years to fund the Scripps Research laboratories of 20 investigators, including Professor Peter Schultz, five scientists moving to Scripps



A $40.7 million grant funds the collaborative study of the complex dynamics of protein-carbohydrate interactions.

Gerald Joyce, Ph.D., was appointed dean of the faculty

Research from GNF, and 14 assistant professors. Terms also facilitate the future funding of Scripps Research faculty by Novartis.

The Consortium for Functional Glycomics, led by Scripps Research Professor James Paulson, received a $40.7 million "glue" grant for the international group of some 300 participating scientists to continue collaborative study of the complex dynamics of protein-carbohydrate interactions. The five-year grant from the National Institute of General Medical Science of the National Institutes of Health (NIH) follows a grant of $34 million awarded in 2001.

The Integrative Neuroscience Initiative on Alcoholism, led by Scripps Research Professor George Koob, won renewal of support from the NIH's National Institute on Alcohol Abuse and Alcoholism. The grant, expected to total $38 million over five years, supports the efforts of a multi-institutional consortium of investigators to identify the molecular basis of alcoholism.

Scripps Research launched a research and educational initiative with McDonald's to drive progress toward a solution to childhood obesity and Type 2 diabetes. McDonald's will contribute $2 million to the institute to address these critical health issues.

PEOPLE NEWS

In 2006, Scripps Research continued to be served by an outstanding group of trustees and administrators.

At our commencement ceremony in May that graduated 31 students from the Kellogg School of Science and Technology, we conferred two honorary degrees in recognition of Hon. Alice Sullivan (Ret.), retiring chair of the Scripps Research Board of Trustees who will continue as a trustee, and Alexander Dreyfoos, also a member of the Board of Trustees.

The business leader and philanthropist John Moores was unanimously elected new chair of the board—he will bring enormous skill and energy to the position. We also have the pleasure of welcoming back Ralph J. Shapiro of Beverly Hills, California, chair of Avondale Investment Company, and welcoming Marjorie Fink of Palm Beach County, Florida, to the board.

With the appointment of Professor Gerald Joyce as dean of the faculty and Professor Jeffrey W. Kelly as dean of graduate and postgraduate studies, in July we formalized a new distribution of administrative responsibilities. This change will enhance efficiency and communication in our academic programs.

Barbara Suflas Noble, who has been part of our administrative team in Florida, will assume the position of director of external affairs for Scripps Florida. Peter Policastro joins our team as senior director of business development for Scripps Florida.

We also welcome investigator John Cleveland, who will head a new Cancer Biology Department on the Scripps Florida campus.

AWARDS AND HONORS

Many awards and honors lauded our faculty, postdoctoral fellows, and graduate students in 2006.

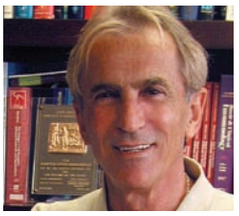
Among the faculty recognitions:

+ Professor Dale Boger was elected to the American Academy of Arts and Sciences. Fellows are selected through a highly competitive process that recognizes individuals who have made preeminent contributions to their disciplines and to society at large.

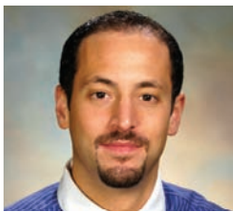
+ Chair of the Scripps Florida Department of Infectology Charles Weissmann received the prestigious DART/NYU Biotechnology Achievement Award from the Biotechnology Study Center of the New York University School of Medicine for his elucidation of multiple interferon genes

Dale Boger, Ph.D., was elected to the American Academy of Arts and Sciences for preeminent contributions to the field of organic synthesis

Clare Waterman-Storer, Ph.D., won the 2006 R.R. Bensley Award in Cell Biology



Professor Argyrios Theofilopoulos, M.D., was honored several times for lifetime contributions to medicine and autoimmune research



Phil Baran, Ph.D., was recognized as an outstanding young researcher

and the pharmaceutical development of Intron A (interferon alpha2b).

+ Chair of the Department of Chemistry K.C. Nicolaou won both the 2006 American Chemical Society Auburn G.M. Kosolapoff Award and Germany's Burkhardt-Helferich Prize. He is also an author of one of Chemical Abstracts Service's 10 most-requested papers (second quarter), "Palladium-catalyzed cross-coupling reactions in total synthesis," in *Angewandte Chemie*.

+ Two patents on "click chemistry" by Professor K. Barry Sharpless, Assistant Professor Valery Fokin, and Associate Professor M.G. Finn were among the Chemical Abstracts Service's 10 most-requested patent families (second quarter).

+ Associate Professor Clare Waterman-Storer won the 2006 R.R. Bensley Award in Cell Biology from the American Association of Anatomists (AAA), which recognized her for innovation in molecular microscopy and contributions to the understanding of cytoskeletal dynamics in cell motility.

+ Professor Argyrios Theofilopoulos was honored several times this year for lifetime contributions to medicine and autoimmune research, receiving honorary doctoral degrees from the Aristotle University of Thessaloniki, Medical School and the Democritos Medical School of Alexandroupolis, as well as election as corresponding member of the Academy of Athens.

+ Professor Bruce Beutler won the Cancer Research Institute's 2006 William B. Coley Award for Distinguished Research in Basic Immunology for his contribution to our understanding of the events leading to the initiation of innate immunity.

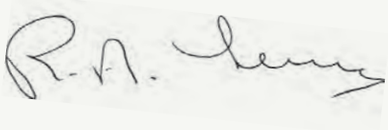
+ Associate Professor Phil Baran received the Sloan Research Fellowship for "outstanding researchers early in their academic careers." He also received the Bristol-Myers Squibb Unrestricted Freedom to Discover Grant (2006 - 2010), and a National Science Foundation CAREER award (2006 - 2010).

+ Norman Klinman, who became professor emeritus this year, received the 2006 Excellence in Mentoring award from the American Association of Immunologists for exemplary career contributions to a future generation of scientists.

Our hardworking postdoctoral fellows were also recognized by numerous grants and awards. As a few examples, Ian Schneider of the Waterman-Storer lab won a Damon Runyon Fellowship Award; Adam Mullick of the Curtiss-Tobias lab, a fellowship from the American Heart Association; Terry Meehan of the Havran lab, a Crohn's & Colitis Foundation of America Research Fellowship Award; and Jeff Lee of the Ollmann Saphire lab, the Canadian Governor General's Gold Medal.

As for our Ph.D. candidates in the Kellogg School of Science and Technology, an unprecedented five students—Dan Bachovchin, Christine Fang, Graham Johnson, Costas Lyssiotis, and Adrian Ortiz—were awarded National Science Foundation Fellowships this year. In addition, students garnered prestigious awards from private donors, the NIH, Novartis, Baxter, and many other organizations, including the Hertz Foundation, the American Heart Association, Achievement Rewards for College Scientists, and the American Chemical Society.

This year's achievements make me proud to be part of The Scripps Research Institute. My congratulations go out to faculty, staff, postdoctoral fellows, students, trustees, and loyal supporters for another year well done.



Richard A. Lerner

"Our vaccine slowed weight gain and decreased stored fat in rats. While food intake was unchanged in all testing groups, those who were given the most effective vaccines gained the least amount of weight."

KIM JANDA, PH.D.

Scripps Research investigators Kim Janda (top) & Eric Zorrilla collaborated on a study that made headlines around the world

Vaccinating Against Obesity

STUDY OFFERS POTENTIAL NEW APPROACH TO COUNTER WEIGHT GAIN AND YO-YO DIETING

The fight against obesity is the story of the year and we have Kim Janda, Eric Zorrilla, and colleagues at The Scripps Research Institute to thank for it. Since the publication of their scientific study in August, articles on their potential obesity vaccine have appeared in more than 100,000 publications worldwide, while hits on the Scripps Research site have numbered in the hundreds of thousands.

Janda, who is Ely R. Callaway Jr. Professor of Chemistry at Scripps Research, member of its Skaggs Institute for Chemical Biology, and director of the Worm Institute for Research and Medicine, has appeared in dozens of interviews including *Good Morning, America* and the *Today Show*. He has talked to the BBC three times; reporters have contacted him from places as disparate and distant as Japan, Australia, Russia, and Ireland—some of whom called at midnight to query him.

"I think I've talked to every news source everywhere," Janda said. "One day I was talking on two phones simultaneously and finally had to drop the cell phone on the floor—it got too crazy!" Janda has now had his allotted 15 minutes of fame and maybe a tad more: "It's been unbelievable. I was in a restaurant the other day and somebody came up to me and asked if I was the obesity guy."

Zorrilla, also a faculty member at Scripps Research, held up his end, speaking with KUSI-TV, network syndicates, Univision, and GMTV (Europe's most-watched morning show), and numerous print and web-based media. "The coverage was honestly more than I anticipated for a proof-of-principle study," Zorrilla said, "but emphasizes both the need and desire for more effective treatments for obesity."

In addition to the media deluge, emails by the hundreds have come into Scripps Research from people asking if they can sign up for clinical trials. Some even sent personal photographs. Everyone, it seems, is looking for the next pill, shot, or other magic bullet that will make them thin… forever.

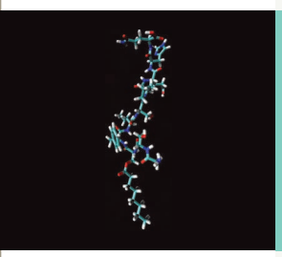
"We really did hit a grand slam on this, not just a base hit," Janda said of the breakthrough study.

A PROMISING NEW APPROACH

What helped make this grand slam possible was the fact that Janda's group has been working through some of the basic science of this approach—immunopharmacotherapy—in other research areas, such as cocaine and nicotine addiction, for the past 20 years.

Also contributing to the score was the stunning failure rate of almost every other pharmaceutical approach to serious weight control.

The old agonist/antagonist types of drugs used to treat obesity were remarkably unsuccessful



Ghrelin is a naturally occurring hormone that helps regulate energy balance in the body.

"When you diet, the body responds as if it was starving and increases the production of ghrelin to stimulate eating and preserve body fat. Our vaccine has the real potential to prevent or seriously reduce yo-yo dieting by interfering with these actions of ghrelin."

ERIC ZORRILLA, PH.D.

at helping people maintain or lose weight. "These drugs are either not effective or are only effective when you're taking them," noted Janda. "When you stop, the weight comes back on."

In contrast, the immunopharmacotherapy approach is based on the idea that the body can be taught to produce antibodies that bind to a target before it can reach the brain. Recognizing a molecule that it ordinarily wouldn't, the immune system can stop some problems in their tracks.

For the treatment of drug abuse, for example, immunopharmacotherapy cuts to the chase: no drug in the brain, no physiological rewards from drug intake. The Janda laboratory has shown that many of the neurophysiological effects of drug use can in fact be alleviated through active vaccination (i.e., immunization with a hapten-protein conjugate; haptens are small molecules that induce antibody formation when bound to a larger carrier protein) or passive immunization (i.e., direct delivery of a monoclonal antibody designed to bind to the drug in question).

With those kinds of tantalizing possibilities in the air, Janda was eager to see if immunotherapy could be used to tackle obesity—which he describes as "soon to be the number one threat to health in the United States."

OBESITY GOES GLOBAL

Obesity is a serious problem for over a billion people worldwide. According to a 2005 report by Trust for America's Health, a non-profit research and watchdog group, approximately 119 million Americans, or 64.5 percent of adult Americans, are either overweight or obese. Worse, according to the report, obesity rates continued to rise "in every state but one, and government policies and actions to date offer little hope of countering the trend."

Obesity is a major risk factor for a number of other diseases including heart disease, various cancers, Type 2 diabetes, stroke, arthritis, and depression. The National Institutes of Health (NIH) estimates that obesity is a contributing factor in nearly 70 percent of cardiovascular disease cases and 80 percent of noninsulin dependent diabetes cases. It more than doubles the risk of high blood pressure and is believed to increase the incidence of stroke and some forms of cancer. The NIH estimates direct costs attributable to our excess pounds at $123 billion, or nine percent of total U.S. health care costs. And some 110,000 deaths a year are due to poor diet and inactivity.

Even though a number of approaches have been tried to help people control their body weight, few have been successful and several, including the drug fenfluramine/fenfluamine, have been pulled from the market by the U.S. Food and Drug Administration.

So, when Janda teamed up with Zorrilla, whose lab focuses on energy homeostatis (see *Endeavor* article, Fall 2006), and they offered a glimpse into the possibility that one day people might be able to slow weight gain and reduce body fat with a simple vaccine, not so different than the ones they get for measles or mumps, this news was greeted with great interest.

It sounded to many like opening Pandora's Box only to find non-fattening jewel-encrusted chocolate bars inside.

A GLIMPSE INSIDE THE BOX

In the study, which was published online August 4 in an advanced, online edition of the *Proceedings of the National Academy of Sciences*, researchers immunized mature male rats with specific types of an active vaccine. Compared with control groups, the immunized rats ate normally, yet gained less weight and burned more fat. These results indicate that the vaccine directly effects the body's metabolism and energy use, and not the digestive system. The vaccine did not produce a systemic inflammatory response, which can also cause weight loss and reduce food intake.

"Our vaccine slowed weight gain and decreased stored fat in rats," Janda said. "While food intake was unchanged in all testing groups, those who were given the most effective vaccines gained the least amount of weight."

This study's findings were especially encouraging because of what is known to every dieter on the face of the earth—the yo-yo effect, the predictable cycle of repeated loss and gain of weight. The new vaccine, which is directed against the hormone ghrelin (pronounced grell-in), a naturally occurring hormone that regulates hunger and energy balance in the body, has shown the ability, in animal models at least, to stop that dangerously futile struggle.

Ghrelin, an endocrine hormone produced primarily in the stomach, plays a physiological role in energy homeostasis, although the full extent of that role remains unknown. It was first identified in 1999 as a naturally occurring ligand—a molecule that binds to another to form a larger molecular complex—for a growth hormone secretagogue receptor. What is known is that ghrelin cycles between meals and thus promotes weight gain and fat storage through its metabolic actions, decreasing the breakdown of stored fat for energy as well as energy expenditure itself. During periods of weight loss such as dieting, the body produces high levels of ghrelin to preserve body fat and encourage eating.

"When you diet, the body responds as if it was starving and increases the production of ghrelin to stimulate eating and preserve body fat," Zorrilla explained. "Our vaccine has the real potential to prevent or seriously reduce yo-yo dieting by interfering with these actions of ghrelin."

The study did note, however, that the immunized rats were relatively lean and were fed low-energy, low-fat and relatively less palatable chow diets. Whether active immunization against ghrelin would help prevent the development of obesity caused by high-fat "Western" diets or whether it would facilitate weight loss once obesity is established remains uncertain.

"Our study was the first real *published* evidence proving that preventing ghrelin from reaching the central nervous system can produce a reduction in weight gain," Janda said. "We're not claiming that our study answers all the questions surrounding the treatment of obesity. What we are saying—and what our study confirms—is that this looks like a serious, workable solution to the problem. And while much more study is needed to understand the full therapeutic potential of immunopharmacotherapy in combating obesity, these initial results are extremely positive."

THE SIDE EFFECTS ISSUE

But the idea of developing therapeutic vaccines itself is not without controversy.

Janda, like other researchers, is concerned about long-term side effects of the team's vaccine candidate. Typical of that concern was the response of Bruce Dan, one-time editor of the *Journal of the American Medical Association*, who pointed out the unknown effects of modifying the immune system to counter a natural reaction. "If you are going to try to protect yourself against the cold it is better to buy a fur coat than to change your genetic system to grow hair," he said.

Janda wondered much the same thing when he suggested that a vaccine may not be the best way to treat obesity.

"No one knows if an active vaccine is the most effective means to control obesity," he said. "With an active vaccine like the one we have currently developed, we don't know what kind of weight loss might happen over the long-term. Once the active vaccine is turned on, you have to wait until the immune response ends. That's why we're looking carefully at this before there's even a hint of introducing it into humans."

In an exciting extension of their research, Janda and Zorrilla have launched studies into passive vaccines to control eating behaviors. "A monoclonal antibody to ghrelin, or what is known as a passive vaccine, might be more effective and more controllable in terms of how long it's in the body," said Janda. The researchers will also conduct investigations with different types of obese animals, and with different types of food, including fat-rich food more typical of the Western diet.

Zorrilla is looking forward to continuing the collaboration. "I really enjoy working with Kim [Janda] and his group members," he said. "Kim and his lab members are highly creative, highly skilled, and highly collaborative. Scripps Research is really a unique place in the collegiality of its faculty and in the willingness of faculty to cross specialized niches in order to undertake interdisciplinary research. The scientific environment promotes collaboration, allowing us to tackle big problems in creative ways."

ERIC SAUTER AND MIKA ONO BENEDYK

"I've met the parents of many children affected with the disease and some of the patients and it would be just a dream to be able to help them."

JOEL GOTTESFELD, PH.D.

Getting to the Root of Friedreich's Ataxia

JOEL GOTTESFELD COMES FULL CIRCLE

Some scientists go through their careers getting more and more focused on smaller bits of knowledge. With science ever-more specialized, the drive to go deeper into a narrow field of study is the only way to stay on top of today's academic game. Other scientists are lucky enough to see their work go the other way, from abstract laboratory findings to real-world results. Joel Gottesfeld, Ph.D., professor of molecular biology at The Scripps Research Institute, has seen his own career go from one extreme to the other.

"I was a basic scientist with my head in the clouds, not thinking about any practical application of my work," said Gottesfeld. "But over the last several years I came to the realization that I could do good—and it's been a transformation."

For Gottesfeld, this has meant finding a way to confront a confounding neurological disease called Friedreich's ataxia.

The progressive, incurable disease affects about 10,000 children and young adults in the United States. The eventual degeneration of the nerve tissue in the spinal cord leaves patients unable to walk, with slurred speech, and later heart disease and diabetes. Most patients die by their early 20s.

Friedreich's ataxia is one of several so-called triplet repeat diseases in which bits of genetic material repeat their nucleotide sequences by the thousands and are therefore unable to encode for certain vital human proteins. There are at least 20 such triplet repeat diseases, including Huntington's disease and fragile X syndrome. In the case of Friedreich's ataxia, the repeats inhibit the production of frataxin, a protein key to the success of the cell's energy-producing mitochondria.

Gottesfeld's interest in Friedreich's ataxia was piqued three years ago while reviewing a scientific paper on the disease for the *Journal of Biological Chemistry*. In passing, the author mentioned that a potential therapeutic might be developed if someone could find a molecule to bind to the nucleotide repeats—in this case GAA—thereby reactivating the gene. Gottesfeld thought that it would be fairly straightforward to build on his own research of many years to put this idea to the test.

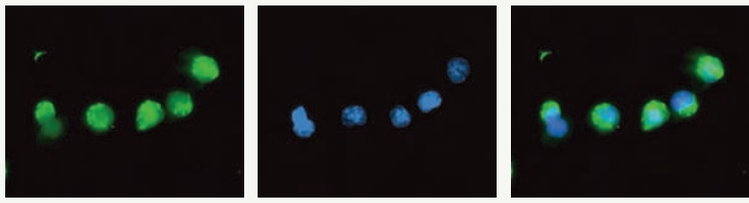
It worked.

BREAKTHROUGH PAPER

Gottesfeld and colleagues published the breakthrough paper on Friedreich's ataxia in August in the journal *Nature Chemical Biology*. →

About one of every 20,000 to 50,000 people in the United States has Friedreich's ataxia, which is caused by a genetic defect that prevents adequate production of the protein frataxin.

Here, images from the Gottesfeld lab show lymphoid cells from a Friedreich's ataxia patient.



In the study, the team tested a variety of compounds that inhibited a class of enzymes known as histone deacetylases in a cell line derived from blood cells from a Friedreich's ataxia sufferer. One of these inhibitors had the effect of reactivating the frataxin gene, which enabled the production of the frataxin protein.

The researchers then went on to improve on this molecule by synthesis of novel derivatives, identifying compounds that would reactivate the frataxin gene in blood cells taken from 13 Friedreich's ataxia patients.

In fact, one of the compounds the researchers tested produced what amounted to full reactivation of the frataxin gene in 100 percent of cells tested.

"They never failed," said Gottesfeld, who goes out of his way to acknowledge the contributions of his lab members, including Research Associates David Herman, Kai Jenssen, Ryan Burnett, and Elisabetta Soragni who were co-authors of the paper. Such therapeutic reactivation of a silenced gene has only been achieved for a handful of other diseases.

Peter Wright, Ph.D., chairman of Scripps Research's Department of Molecular Biology, commented, "It's extremely important work. The targeting of specific genes is [Gottesfeld's] approach, and it's a different approach than what everyone else has been doing. It's very promising."

"I've met the parents of many children affected with the disease and some of the patients," Gottesfeld said, "and it would be just a dream to be able to help them."

A NEW THEORY

While other labs across the country are working on rehabilitating the mitochondrial function that is blocked in Friedreich's ataxia and several drugs are now in clinical trials, Gottesfeld wanted to attack the cause rather than the symptoms.

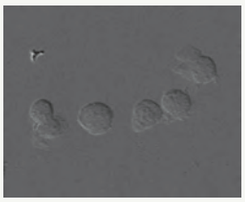
To do so, he drew on a new theory of why the triplet repeats prevent transcription of the frataxin gene in Friedreich's ataxia, although the gene itself remains intact. This explanation is known as the "histone code theory."

Histones are proteins that are the chief constituent of the nucleosomes around which DNA is wrapped in cells. The new theory suggests that histones must contain certain chemical cues, including acetyl groups, for nucleosomes to assume the formation that allows the genes they package to be expressed.

The paper's authors suggest that the triplets cause an unusual DNA structure that attracts proteins such as histone deacetylases (HDACs), removing critical acetyl groups from the histones, packaging the histones in an inactive form called heterochromatin, and ultimately silencing the frataxin gene.

Based on this theory, Gottesfeld and colleagues attempted to reactivate frataxin production with compounds that might block the HDACs. Luckily, a range of such products was commercially available, as many HDAC inhibitors have been developed as tools for molecular biology research and as potential cancer treatments.

Importantly, the team's HDAC inhibitors have proven uniformly non-toxic to the blood cells



"They never failed."

JOEL GOTTESFELD, PH.D., on an experiment that reactivated the frataxin gene in blood cells.

used in the study and do not significantly affect cell growth rates. Ongoing animal studies also have not revealed any toxicity. If the results of animal testing remain positive for safety and efficacy, said Gottesfeld, the HDAC inhibitors could enter human trials as a Friedreich's ataxia treatment in as soon as 18 months' time.

BACK TO THE FUTURE

In some ways, Gottesfeld has come full circle in his journey from basic research to investigations with an applied bent. Growing up in Los Angeles, and as an undergraduate at the University of California, Berkeley in the late 1960s, Gottesfeld was set to follow other family members and become a doctor. By his sophomore year, though—as protests rocked the campus and Gottesfeld found himself tear-gassed between classes—it was time for a change.

He found a mentor of sorts in Nobel laureate Melvin Calvin, who taught organic chemistry. Even though classes were held in a crowded lecture hall, Gottesfeld often stayed afterward to talk science, including Calvin's research in biochemical reactions of photosynthesis. Through persistence, Gottesfeld convinced Calvin to give him a summer job in his lab. That cinched it. Science trumped medicine. The hard part was convincing his parents, who actually drove up from Los Angeles to change the young Gottesfeld's mind.

"They were totally appalled," Gottesfeld remembers. "There had never been a scientist in the family before."

A meeting between mentor and parents was called, and Calvin convinced them that Gottesfeld had a bright future as a scientist. His parents relented, and Gottesfeld finished Berkeley with a degree in biochemistry. A Fulbright fellowship to Oxford University followed.

There, he lived and studied at Merton College, one of the ancient colleges at Oxford founded in 1264. During university holidays, when British students went home and the campus was quiet, Gottesfeld often dined with one of the school's visiting resident fellows, an 80-year-old English lit teacher named J.R.R. Tolkien. By 1972, Tolkien's "Lord of the Rings" trilogy had become a cultural icon, and was read by just about every backpack-toting college student in the 1960s, Gottesfeld included. Tolkien died later that year, and Gottesfeld notes one of his prized possessions is an autographed copy of "The Hobbit."

ANOTHER PATH

Despite Oxford's prestige and tradition, Gottesfeld saw his path elsewhere. The university's use of nuclear magnetic resonance technology as a tool for exploring molecular biology wasn't sufficiently developed at the time, says Gottesfeld, so he instead opted to enter the doctoral program at the California Institute of Technology (Caltech).

There, Gottesfeld became part of an exciting lab run by James Bonner, who was exploring the various functions of chromatin, which is the DNA plus the histone proteins (and RNA) that package

A Longstanding Interest in DNA

In his early days as a Fulbright fellow at Oxford University, Joel Gottesfeld was attracted to a dusty jar in a back room. The jar contained a DNA sample dating back to the 1950s that is believed to be from one of the earliest DNA extractions.

"It's extremely important work. The targeting of specific genes is [Gottesfeld's] approach, and it's a different approach that what everyone else has been doing. It's very promising."

PETER WRIGHT, PH.D.

Scientist Joel Gottesfeld (center) and his research team: (L-R) Elisabetta Soragni, Kai Jenssen, Ryan Burnett, and David Herman.

DNA within the cell nucleus. Chromatin is important for relaying transcription information to messenger RNA for recombination and for DNA repair. Bonner theorized that histones, instead of just serving as a structural component of the double helix, actually had an active role in regulating gene function.

"Bonner was one of the first people to recognize the importance of the histone proteins in gene regulation rather than just as a passive glue," says Gottesfeld, whose research still builds on that insight today.

Gottesfeld continued working on chromatin during his doctoral thesis at Caltech, and again at Cambridge, where he landed a postdoctoral fellowship at the MRC Laboratory of Molecular Biology.

His return to Great Britain, this time for three years, gave Gottesfeld the opportunity to meet another influential scientist—this time the godfather of DNA, Francis Crick. Crick was chair of the department in Cambridge, and for about 18 months, the two talked frequently, often about the role of chromatin. While Gottesfeld is an easy-going Southern Californian, Crick could be brash and immodest, sometimes rubbing colleagues the wrong way. Not Gottesfeld.

"He made science so much fun," Gottesfeld said. "He didn't tolerate stupid ideas one bit and he would let you know when he thought you had a stupid idea. And you had to be able to take it. He liked discussions and arguments. I was young and cocky enough to get along with him well."

Crick also helped Gottesfeld get a job at Scripps Research in 1978, where Gottesfeld later became one of the first members of the Department of Molecular Biology.

BUILDING ON BASIC BIOLOGY

Over the years, Gottesfeld has seen his interests evolve from "card-carrying molecular biologist" into a new hybrid that includes a powerful dose of chemistry.

Since the mid-1990s, Gottesfeld has focused on gene expression, more specifically how to bind small molecules that can be synthesized at will to read any particular DNA sequence. This was made possible with a long-term collaboration with Peter Dervan, an organic chemist at Caltech. Their first success came in using this method to find cancer-fighting agents.

"We found a molecule that binds to a DNA sequence in a gene expressed in a wide range of different cancers," Gottesfeld explains. "This molecule turns this gene off. We've identified a molecule that blocks the growth of cancer cells. Using a microarray experiment, when we looked at a variety of human cancers, we found that the gene was over-expressed in many human cancers, and that this molecule will down-regulate in many kinds of cancers."

Gottesfeld and Dervan have shown the method has efficacy in colon cancer, chronic myelogenous leukemia, and prostate cancer cell lines. Further animal studies are necessary before the molecule can enter human clinical trials.

Using a similar approach, Gottesfeld has been forging ahead with research on Friedreich's ataxia. This endeavor has been made all the more relevant by meeting parents and victims of the disease through the Friedreich's Ataxia Research Alliance (FARA), which has also funded his research.

"These people are grasping at straws for essential therapies," Gottesfeld said. "They are so pleased to find scientists out there working on the disease because it's not well known."

Raychel Bartek, a member of the group and mother of a child suffering from Friedreich's ataxia, has been eagerly following the scientific developments at Scripps Research.

"We know [a therapy] is a long way off," she said from Arlington, VA. "But the whole Friedreich's community is very excited."

ERIC NIILER AND MARK SCHROPE

"Structures can tell us about function and evolution and how we might use that information to design drugs, better catalysts, or even vaccines."

IAN WILSON, D. PHIL.

Structures Working For and Against Us

IAN WILSON REVEALS THE SHAPE OF PRESENT AND FUTURE PANDEMICS

Ian Wilson has had another big year. Not only did his work shed light on the threat of an avian flu pandemic and other hot topics, he presided over the opening of a new facility at The Scripps Research Institute that puts him on the fast track to solve even more critical biological structures, faster.

Why focus on structures? The architecture of a molecule can offer tantalizing clues about our basic biology, health, and disease—including how we might combat some of the major scourges of the modern world.

"Structures can tell us about function and evolution and how we might use that information to design drugs, better catalysts, or even vaccines," says Ian Wilson, D. Phil., who is a professor at Scripps Research, a member of its Skaggs Institute for Chemical Biology, and principal investigator for the Joint Center for Structural Genomics.

BIRD FLU ALERT

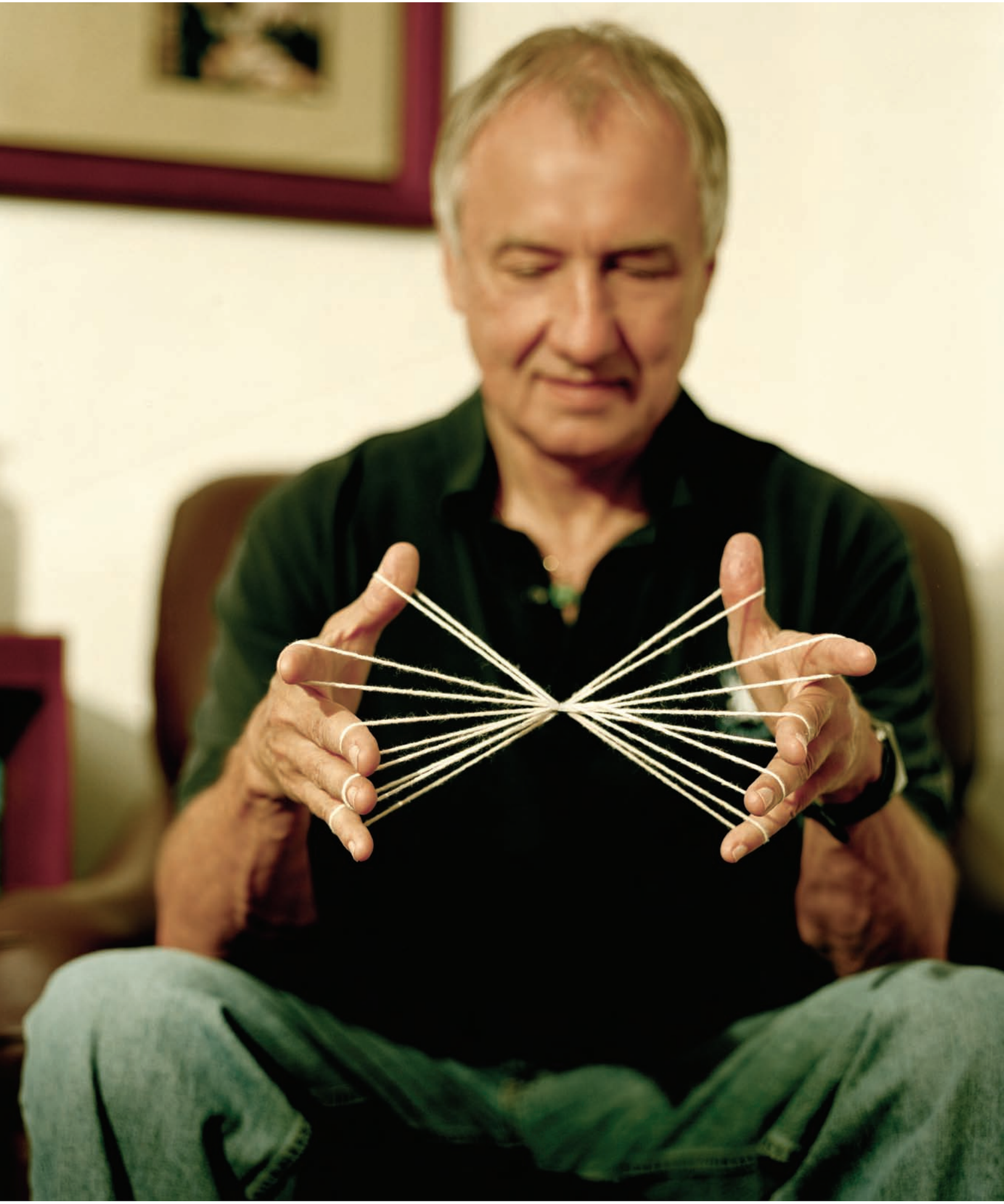
Take bird flu—near the top of the list of concerns for infectious disease experts today.

So far, the disease has been largely a disease of poultry and wild birds, with its impact mainly an economic one as infected flocks have been culled. An estimated 150 million birds have either died of the disease or been killed in an attempt to stop its spread.

But the greater worry is that the virus may not stay in birds. To date, the spread to humans of the H5N1 avian influenza virus—the strain of current concern—has been limited, with some 240 documented severe infections and 140 deaths in Indonesia, Vietnam, Thailand, Cambodia, China, Iraq, Turkey, Egypt, Djibouti, and Azerbaijan as of August 2006, according to the World Health Organization.

But these cases are troubling. For one, the high mortality rate confirms that our immune systems are ill prepared to combat pathogens derived from other hosts. While most new influenza strains come to humans from other animals, for example pigs, our immune systems are particularly unprepared to fight off viruses that make the more unusual jump directly to humans from birds.

According to Wilson, this could be what happened in 1918, when the terrible epidemic known as the Spanish Flu swept the world. This outbreak took more lives than World War I and became the largest and deadliest influenza outbreak in recorded history, killing 675,000 in the United States and up to 40 million worldwide. →



"The potential for the emergence of a human-adapted H5 virus, either by reassortment or mutation, is a clear threat to public health worldwide."

IAN WILSON, D. PHIL.

Now, as new cases of bird flu make the headlines, the public is increasingly aware of the current threat from an outbreak of bird flu. Earlier this year, a poll by Harvard School of Public Health reported that more than 60 percent of Americans are concerned about the possibility of a bird flu epidemic.

But are today's concerns overblown? Could the particular strain of bird flu now appearing in Asia and Central Europe ever fully cross species lines to become a communicable disease in humans?

A CLEAR AND PRESENT DANGER?

Wilson and colleagues set out to assess the risk.

An avian influenza could transform into a disease contagious among humans in one of two ways. It could evolve through mutations—and infectious viruses are constantly mutating. Or, in a case where a person is infected with a human flu and the bird flu at the same time, the two viruses could swap genes—reassort—creating a new flu variation.

Collaborating with the Consortium for Functional Glycomics, led by Scripps Research Professor James Paulson, Wilson and colleagues compared a number of avian and human viruses, including rare samples from the 1918 influenza outbreak, to gauge how adapted various avian influenza strains are for entering human cells.

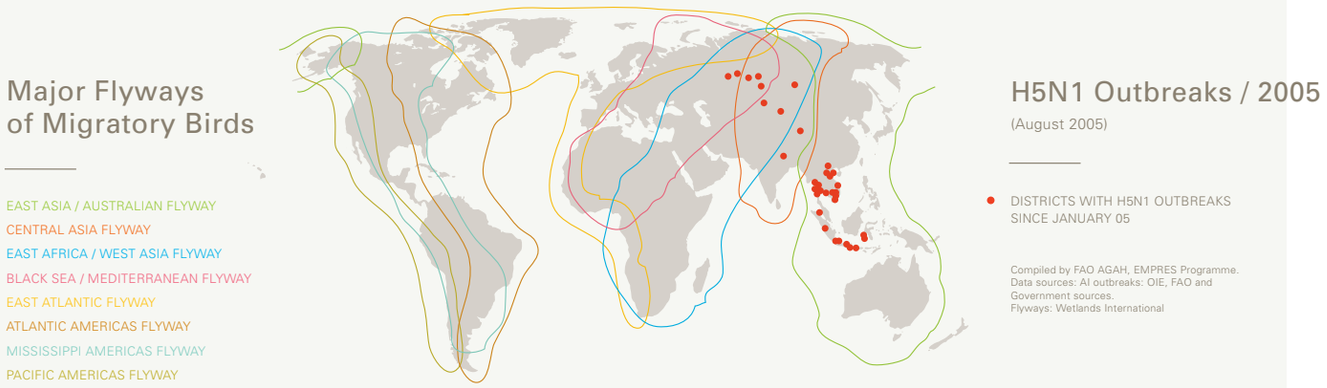
To do this, they used a new technology developed by the Consortium for Functional Glycomics called a glycan array, a grid of sugars resembling those found on the outside of human cells. This enabled the researchers to look at the specificity with which the influenza proteins bind to these sugars. By including closely related recombinant forms of these proteins in the study, the team was able to identify specific amino acid changes responsible for shifting the influenza virus's specificity.

"It would appear that two mutations could change the specificity dramatically going from avian to human for the 1918 virus," Wilson noted in January, when the study was published in the *Journal of Molecular Biology*.

In March, in collaboration with the Centers for Disease Control, the researchers followed up with a paper in the journal *Science* describing a specific possible pathway that could enable a particularly virulent subtype of the H5N1 virus, isolated from a 10-year-old Vietnamese boy who succumbed to the infection in 2004, "to gain a foothold in the human population."

The paper showed that a relatively small number of mutations to the hemagglutinin gene—the "H" in the H5N1—resulted in partial switching of the binding site preference of the avian virus from receptors in the intestinal tract of birds to the respiratory tract of humans.

"The potential for the emergence of a human-adapted H5 virus, either by re-assortment or mutation, is a clear threat to public health worldwide," said Wilson. "One piece of good news, however, is the glycan array could prove invaluable in the field for monitoring signs that bird flu has developed the



capability of crossing the species barrier."

While the avian flu was the big story for Wilson this year, his lab has been making significant contributions to a wide variety of basic and applied topics. In February, in collaboration with Scripps Research Professor Kim Janda (see article, page 6), the lab shed light on a cocaine-degrading monoclonal antibody Fab' fragment, important for the chain of events that breaks cocaine into nontoxic pieces. The Wilson group also recently solved several crucial immune system structures, including TLR3 and CD1a.

And, in other notable work, the lab has made key contributions to the effort to develop an AIDS vaccine (see Winter 2003 *Endeavor* story, "It Had to Work"). Collaborating with Scripps Research Professor Dennis Burton, who heads a scientific consortium of the International AIDS Vaccine Initiative, the team has now helped solve the structure of three antibodies—b12, 2G12, and 4E10—that effectively neutralize human immunodeficiency virus (HIV), the virus that causes AIDS. The huge potential public health impact of this work, published in 2001, 2003, and 2005, is still being played out.

THE POWER OF PERSISTENCE

This string of successes from the Wilson lab is no accident. Wilson has been demonstrating unusual tenacity and scientific acumen since he entered the field.

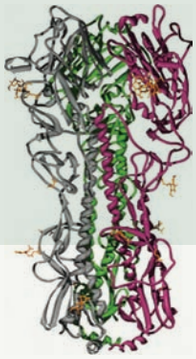
After earning his B.Sc. in Biochemistry from the University of Edinburgh in 1971 (Wilson grew up in Scotland), and his D. Phil. from the University of Oxford in 1976, Wilson was given a prestigious fellowship to continue structural work in the large, well-established Oxford laboratory of his mentor David Phillips.

Yet, after a few months, he chose to leave it behind for the startup lab of Don Wiley at Harvard University. In fact, Wilson arrived as the only other full-time member of the lab other than Wiley himself and a graduate student.

What lured Wilson there was what he recognized as the potential of a particular research project—the attempt to use x-ray crystallography to determine the structure of the protein hemagglutinin from a strain of influenza virus. As Wilson's recent work on the bird flu has underlined, hemagglutinin is now recognized as the major virulence factor associated with the virus.

In x-ray crystallography, the technique that still underpins Wilson's work today, scientists manipulate a protein or some other molecule so that a crystal forms. This crystal is then placed in front of a beam of x-rays, which diffract when they strike the atoms in the crystal. Based on the pattern of diffraction, scientists can reconstruct the shape of the original molecule.

But by today's standards, the technology was primitive. Wilson recalls the crystals weren't good, the diffraction was poor, and it was difficult to make accurate measurements. Moreover, computer sup-



Ribbon representation of the hemagglutinin HA0 trimer from the 1918 influenza virus.
Image courtesy of James Stevens.

FINDING ANSWERS THROUGH STRUCTURES

A structure from the virus that caused the 1918 Spanish Flu—the largest and deadliest influenza outbreak in recorded history—suggests that it originated in birds.

port was extremely limited, consisting of sending data over an unreliable telephone line to Columbia University during off hours—which meant that was what Wilson was doing most nights until 6 AM.

After four years of painstaking work, some of it carried out by hand, the researchers submitted two papers to the journal *Nature*. Remarkably, the editors accepted both papers without change—which, in science, happens about as often as golfers hit two holes-in-one.

Wilson arrived at Scripps Research in 1982, shortly after the completion of the project. With no structural community, no biophysics, and little molecular biology, the institute at first seemed to have little to recommend it. But Wilson saw something he liked.

"Richard Lerner [then a member of the faculty, now president] was proposing to set up a new Department of Molecular Biology with structure as a key component," Wilson says. "The opportunity to be part of an exciting new venture where one could help choose one's colleagues as well as help shape the direction of the department was a big opportunity for a starting assistant professor. The resources that were being allocated to set up crystallography and computing facilities at Scripps were too good to ignore. Furthermore, Richard's vision to highlight structure as a centerpiece of the new department was a bold move at that time and was very compelling to me."

A TALENT FOR TEAM-BUILDING

As Wilson's calculated risk again paid off and a thriving community of scientists grew up around him, he has had the opportunity to demonstrate other skills key to his recent successes—a talent for collaboration and team building.

Recently, these qualities have been in the spotlight as principal investigator of a group called Joint Center for Structural Genomics (JCSG), which draws on more than 70 researchers from Scripps Research, the Genomics Institute of the Novartis Research Foundation, the University of California, San Diego, the Stanford Synchroton Radiation Laboratory, and the Burnham Institute.

Created in 2000 in response to the National Institutes of Health's nationwide initiative on protein structure determination, called the Protein Structure Initiative, the JCSG was one of nine centers initially receiving funding in the first phase of the program. In 2005, the JCSG was selected as one of only four centers to advance from the pilot stage to become a large-scale production center.

"The JCSG has highlighted how science can benefit from formation of large consortia to tackle huge scientific problems," says Wilson. "The use of

"The use of high-throughput tools and robotics for experimentation, coupled with bioinformatics, is very powerful and enables problems to be tackled on an unprecedented scale."

IAN WILSON, D. PHIL

high-throughput tools and robotics for experimentation, coupled with bioinformatics, is very powerful and enables problems to be tackled on an unprecedented scale. The structural genomics centers have shown how these high-throughput methodologies and techniques can be exported back to the general scientific community to facilitate biological, chemical, and biomedical research in individual laboratories."

The high-throughput methods the group has developed brings the technique of x-ray crystallography to a new level. Instead of varying conditions, such as temperature, ionic strength, protein concentration, buffer, and pH one by one (which can take months, with no guarantee of success), scientists can run dozens of conditions at once to see if any work.

"With robotic crystallization, you can do things faster, more reproducibly, and with much smaller volumes of protein," says Wilson. "This makes a huge difference."

INCREASING THE ODDS

And now, thanks to support from the Protein Structure Initiative, the International AIDS Vaccine Initiative, and Scripps Research, a dedicated robotic crystallization facility opened in May on the Scripps Research La Jolla campus.

Built as a model system by Carlsbad company RoboDesign (since acquired by Rigaku/MSC, Inc.), the machine is one of the largest of its kind, with storage capacity for 4,000 plates at up to six different temperatures as well as fully automated imaging, scheduling, and analysis software.

"Robodesign offered a fully integrated project," says Research Programmer Marc-André Elsliger of the Wilson lab, who manages the JCSG's Administrative Core. "We didn't have to buy components from different vendors and worry about having them work together."

In fact, the new system is so automated and integrated that scientists can put a sample of protein in at one end, and, if all goes well, some days later pick up high quality crystals to solve the structure—a far cry from how x-ray crystallography was done in Wilson's early days as a scientist.

The new facility will help Wilson and colleagues meet their ambitious goal of solving between 100 and 200 structures a year—about one every three working days. While no one knows exactly which structures will yield their secrets next, the odds are good that more breakthroughs are on the way.

MIKA ONO BENEDYK

"Human beings will always come up against infectious agents that evolve strategies for their survival, often at the cost of our health."

MICHAEL OLDSTONE, M.D.

Fishing in Troubled Waters

MICHAEL OLDSTONE REELS IN CLUES TO THE RAVAGES OF PRION DISEASE

For more than a century, accepted scientific dogma held that only bacteria, viruses, fungi, and parasites could cause infectious diseases. During the past 50 years, however, evidence accumulated of an infectious disease of another kind.

Termed "transmissible spongiform encephalopathies", these include fatal neurodegenerative diseases of humans and animals—kuru and Creutzfeldt-Jakob disease in humans, scrapie in sheep and goats, mad cow disease in cattle, and chronic wasting disease of deer and elk. The cause most likely lies with abnormally folded infectious proteins—dubbed "prions"—with the bizarre ability to cause their normal counterparts to change their shape, transforming them into deadly biological bullets with a latent capacity to kill. A susceptible person eating prion-tainted beef, for example, could succumb to a dementia-like disease years, even decades, later.

Because the diseases caused by infectious prions lay waste to brain tissue, scientists and physicians have thought of them as chronic neurological conditions affecting only the central nervous system. But in July, a team led by Scripps Research Institute Professor Michael Oldstone, M.D., announced it had discovered infectious prion protein in the hearts of mice previously infected with scrapie in the brain. Infectious prions found outside the brain raised the possibility that heart infection could be a new aspect of prion diseases in both humans and animals.

NEW TERRITORY

In the study, which appeared in the journal *Science* on July 7, 2006, Matthew Trifilo, Ph.D., a postdoctoral fellow at Scripps Research, along with Oldstone and colleagues, virologist Bruce Chesebro, M.D., at the National Institutes of Health (NIH) Rocky Mountain Laboratory, and cardiologist Kirk Knowlton, M.D., at the University of California, San Diego (UCSD), reported that 300 days after laboratory mice were infected with scrapie in the brain, the animals exhibited the telltale misfolded prion proteins in their hearts, along with amyloid, a protein deposit associated with tissue degeneration. Knowlton found these prions with amyloid deposits stiffen the heart and impede its ability to pump blood, similar to human amyloid heart disease.

Unusually high levels of scrapie prions were also identified in the blood of the same mice used in the heart study. "This was the first time prion disease agents were found reproducibly and reliably in large amounts in the blood," says Oldstone,

Abnormally folded infectious proteins—dubbed "prions"—have the ability to cause their normal counterparts to change their shape, causing disease and death years after initial infection. This illustration shows a proposed structure of an abnormal prion.

"No one knows whether the human cases [of prion disease] we've seen have come at the end of an outbreak, or whether we will be seeing many more cases as time goes on."

MICHAEL OLDSTONE, M.D.

whose eminent viral-immunobiology laboratory at Scripps Reserach consists of more than 16 researchers, six working directly with Oldstone and three other independent research groups. "This finding could help scientists to answer basic questions such as how prions travel in the bloodstream—for example, linked to a carrier protein. In addition, the discovery may help in the development of a blood test to identify prion diseases, and possibly a way to filter or chemically treat blood to remove infectious prions."

Because no test to detect prions in the blood currently exists and the disease can be acquired through contaminated blood or blood products as well as by eating tainted meat, many potential blood donors are turned away. Any resident of the United States who lived in England for more than three months from 1980 to 1996, when that country experienced a major outbreak of mad cow disease, or in many other European countries for five years or more, is prohibited from donating blood. In England, only people born after the mad cow outbreak may donate.

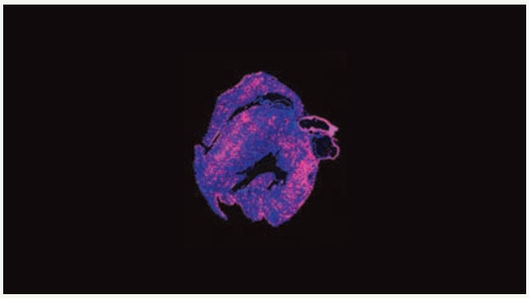
"This has a major economic impact because England is forced to import a significant amount of its blood supplies," Oldstone says. "In addition, blood collections in the United States have been decreased by about 10 percent."

PRIONS: MYSTERIOUS AND DANGEROUS

Prions—the word is a combination of "proteinaceous" and infectious"—were discovered by Stanley Prusiner, M.D., of the University of California, San Francisco, who received a Nobel Prize for his work in 1997. Prusiner's work was at first treated with incredulity—how could proteins that lack DNA and RNA and are not able to reproduce actually replicate in the body of a human or animal? Prions, it seems, are biologically unique, existing somewhere in an area between living and nonliving matter. They are believed to replicate by forcing normal prion proteins to adopt the abnormal shape of the harmful prion protein in a chain reaction-like process.

Prions are normally found throughout the body, even in healthy people and animals; it is only when a normal prion comes into contact with an infectious prion that disease may result. Since infectious prions are copies of a normal protein, the body does not mount a typical immune response against them. They are nearly indestructible, resistant to proteases—the enzymes in the body that can normally break down proteins—and are killed only at extremely high temperatures or with very strong chemicals, methods that harm living tissue. Although scientists hypothesize that normal prions may serve a useful purpose, such as sleep regulation, temperature control, or perhaps memory, their function in the body is still not understood.

Humans who eat meat from infected cattle or who otherwise absorb the abnormal protein may contract the human form of mad cow, new variant Creutzfeldt-Jakob disease. Creutzfeldt-Jakob, named for the German scientists who first diag-



A New Aspect of Prion Disease

Because the diseases caused by infectious prions lay waste to brain tissue, scientists and physicians have thought of them as chronic neurological conditions affecting only the central nervous system. But in July, researchers published a study showing abnormal prion protein in the heart.

nosed it, is a neurological disease that most often strikes older people, causing dementia, memory loss, hallucinations, seizures and eventually, death. New variant Creutzfeldt-Jakob causes similar symptoms, but strikes much younger people, often in their 20s and 30s.

"Normal proteins must be in specific configurations in order to function properly," Oldstone says. "Mad cow demonstrates that infectious animal protein can convert normal human protein into malfunctioning protein that both loses its ability to do its job and is infectious. The question now is whether there will be other similar cross-species jumps as has occurred in cattle and humans." One area of particular concern is meat of infected deer and elk, which may be able to transmit the disease to humans.

Although cases of prion disease in humans are, so far, extremely rare—to date, there have only been about 150 confirmed and probable cases of new variant Creutzfeld-Jacob disease worldwide—they are worrisome because of the long incubation period before the disease manifests. There is no vaccine to protect against infection, and no known drug stops the progress of the spongiform degeneration once it begins.

"No one knows whether the human cases we've seen have come at the end of an outbreak, or whether we will be seeing many more cases as time goes on," Oldstone says. "It is a concern that kuru in Fore natives of New Guinea [who engaged in cannibalism as part of religious rites] has now been reported 50 years after initial exposure."

INTERRUPTING PRION INFECTIVITY

This latest research on prions and heart amyloidosis follows a novel finding in 2005 by Oldstone's group, in collaboration with Chesebro, that a variant form of prion protein that lacked an "anchor" on the cell membrane may be unable to signal cells to start the lethal disease process. The prion protein is normally anchored, or attached, to the cell's surface by a glycosylphosphatidylinositol (GPI) anchor.

In the study, the research team exposed two groups of six-week-old mice to different strains of the agent that causes scrapie. Within 150 days of being inoculated with scrapie, all 70 mice in the control group whose prion protein is anchored to the cell's membrane showed visible signs of infection—twitching, emaciation, and poor coordination—as well as abnormally folded infectious prion protein. These mice died in 160 days. In contrast, 128 mice, similarly inoculated with scrapie, that had been engineered to produce prion protein without a cell membrane anchor exhibited no signs of clinical prion disease. These mice lived a normal lifespan of between 500 and 700 days. Subsequent biochemical and microscopic examination confirmed, however, the animals produced an abnormal form of prion protein and this protein could transmit disease to normal mice.

"The diseased brain tissue resembled that found in Alzheimer's disease," says Eliezer Masliah, M.D., head of neuropathology at UCSD and a col-

"A scientist can develop his or her potential at Scripps because it's a place that encourages an individual's imagination to soar."

MICHAEL OLDSTONE, M.D.

laboratory on the study. Oldstone adds, "Previously, most researchers thought plaques and abnormally folded prion proteins were the toxic component of TSE disease that kills neurons. Our studies show, however, that the abundant deposits of abnormally folded prion protein *per se* may not cause disease, but rather signaling via nerve cell membranes may be important in the disease process."

This ongoing research could eventually alter scientists' views on how to prevent prion diseases, shifting emphasis toward preventing interactions with prion protein anchored to cells.

A CAREER BATTLING INFECTIOUS DISEASE

Born in New York City, Michael Oldstone became interested in medicine as a young boy after reading the classic *Microbe Hunters* by Paul de Kruif, which dramatizes the pioneering bacteriological and virologic work of such scientists as Louis Pasteur. After graduating from the University of Alabama in Tuscaloosa, where he studied literature and history as well as science, and from medical school at the University of Maryland, in 1966 Oldstone landed a postdoctoral fellowship at Scripps Research— where he is still playing out his career.

At Scripps Research, Oldstone began working at the interface of virology and immunology—in fact, he was one of the first scientists at the institute to work with viruses (in his case, the viruses that cause lymphocytic choriomeningitis and measles) to try to understand the lack of effective immune response in persistent viral infection. Oldstone continues to study these viruses; his findings have been used by scientists studying other infectious diseases such as AIDS.

Oldstone lauds Scripps Research for being the type of place where scientists can explore biomedically important questions in an intellectually fertile environment. "A scientist can develop his or her potential at Scripps because it's a place that encourages an individual's imagination to soar," says Oldstone. "Scripps enables the many superb scientists who work here to do the best science possible."

Oldstone—who is now a member of the Institute of Medicine of the National Academy of Sciences and the recipient of numerous awards including the J. Allyn Taylor International Prize in Medicine, the Abraham Flexner Award, and the Pioneer in Neurovirology Award—also enjoys life outside the lab, bird watching, body surfing, reading, and fishing. A fly fisherman whose motto is, "If you want to catch trout you need to cast in a pool where the trout are," Oldstone often fishes in Montana with Chesebro, a friend as well as scientific collaborator.

In addition to editing textbooks about viruses, Oldstone has written a book for the general public, *Viruses, Plagues and History* (Oxford Press, 1998), favorably reviewed by *The New York Times* Sunday Book Section. The work focuses on several of the most famous viruses humanity has come up against—smallpox, polio, measles, yellow fever, and influenza—as well as the diseases that have captured headlines in more recent years, including Ebola and other hemorrhagic fevers, hantavirus, AIDS, and mad cow disease. Oldstone writes about how these have wiped out cities and molded civilizations, and the role scientific research has played in taming these threats.

As a scientist with an abiding fascination for his subject, Oldstone says prion diseases are only among the latest of mankind's infectious foes.

"Human beings will always come up against infectious agents that evolve strategies for their survival, often at the cost of our health," says Oldstone. "Our job as scientists is to do our best to understand and outwit these tiny, natural predators and to train the next generation of researchers to continue this effort."

ANNA SOBKOWSKI

Commencement Celebrates Vitality, Inquisitiveness, Innovation

On Friday, May 19, The Scripps Research Institute held its 14th commencement, celebrating 31 graduating students and honorary degree recipients Hon. Alice Sullivan (Ret.), former chair and current member of the Board of Trustees, and Alexander Dreyfoos, member of the Board of Trustees.

"In ways that the founders of this program had not anticipated, the graduate program has brought a spirit of vitality, inquisitiveness, and innovation to the institute," said Jeffery Kelly, dean of graduate and postgraduate studies. "Our students make us enormously proud."

Earning 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. With 31 graduates, this year's class is among the largest in the institute's history.

At the ceremony, held in the Neurosciences Institute auditorium, the two honorary degree recipients—whom President Richard Lerner described as exemplary leaders—passed on their advice to the new graduates.

Dreyfoos, a resident of West Palm Beach, Florida, emphasized the importance of doing what you love and encouraged the graduates to take advantage of opportunities for networking and collaboration.

Dreyfoos owns and directs The Dreyfoos Group, a private capital management firm that grew out of his previous ventures, including Photo Electronics Corporation and WPEC-TV-12 of West Palm Beach. He was elected to the Scripps Research Board of Trustees in February 2004. Later that year, he and his wife, Renate, announced a gift of $1 million to the institute.

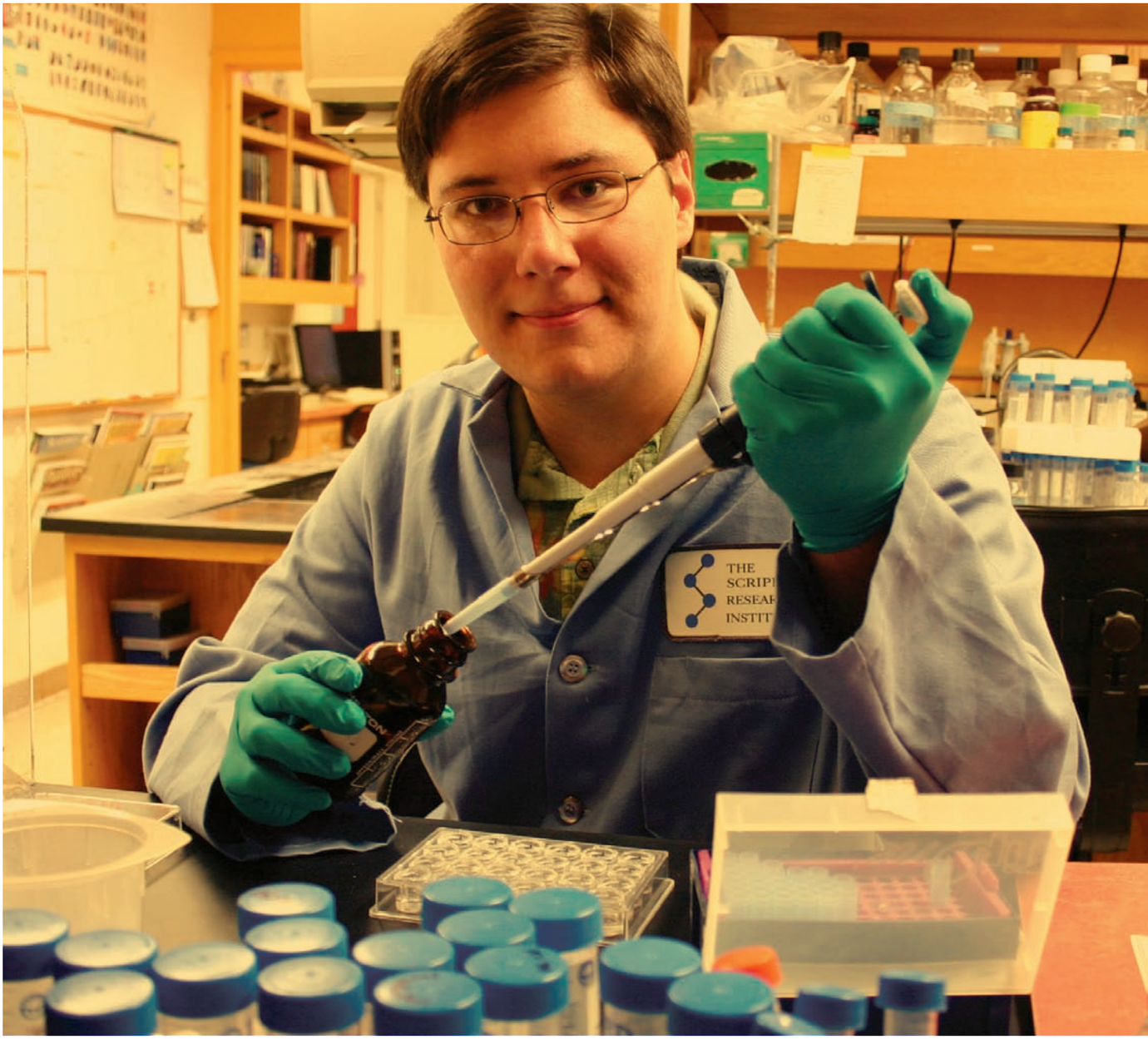
In her address to the graduates, Sullivan emphasized the importance of an open mind, illustrating her point with an image that could be viewed as either a young or old woman.

"History abounds with chance discoveries, important scientific achievements by researchers whose perception allowed them to see what others had not," she noted. "So, when you look in your Petri dish, or mass array, or at your computer screen, remember to look not just for what you expect, but also for the surprises. Take note of what isn't there as well as what is."

Sullivan, formerly judge on the California Superior Court, is founder and chief executive officer of Private Judge, a firm in San Diego that provides expertise in the resolution of business disputes, particularly in the life sciences and technology fields. Elected to the Board of Trustees in 1995, she chaired the group from 2003 to 2006, a period when Scripps Research expanded to Florida, was a leader in federal grant revenue, and founded the first joint doctoral degree program with Oxford University.

This year's graduating students, who were honored individually at the ceremony, have gone on to hold positions in academia and industry, including at Stanford University, the University of California (Berkeley and San Francisco), The Rockefeller University, Sloan-Kettering Institute for Cancer Research, Nagoya University, the California Institute of Technology, the University of Stockholm, and Genentech.

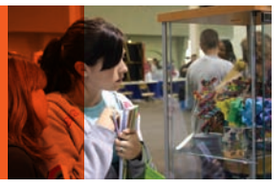
Voices From the Education and Outreach Programs



A Life-Long Love of Science

For some students, one summer experience sparks a life-long love of science. Justin Chartron, shown here, has kept returning to the Stout lab since his internship as a high school student in 2001—not only in high school, but also throughout four years of college at the University of California, San Diego, and acceptance to the California Institute of Technology, where he will begin a graduate program in biology in the fall.

listen



explore

The Scripps Research Institute's outreach programs in California and Florida spark an interest in science among young people and encourage them to consider careers in the life sciences. From career fairs to internships, from teacher training to lab tours, the initiatives reach out to share the thrill of discovery and the rigor of the scientific enterprise.

Here's what people are saying about this year's activities:

Matthew Poling, graduating senior at Steele Canyon High School, now attending the University of California, San Diego.

"[My summer] project was not only very fun, it was very interesting and allowed me to learn so much more about biology and biological research—things that you just couldn't learn from a textbook. It was an amazing experience."

Ashley Wells, 11th grade student at Palm Beach Gardens High School, who plans to major in microbiology at the University of Florida.

"The summer internship at Scripps [was] a fantastic way to gain experience and further my knowledge…"

Todd Linke, Instructor of biology and honors science research, Mt. Miguel High School, San Diego.

"[The Science Partnership Scholars Program] greatly enhanced my classroom instruction... providing me with information on biomedical research from researchers on the 'front line.'"

Sherry Bowen, Living Science Coordinator for Indian River Community College, to Harry Orf, Scripps Florida's vice president for scientific support operations.

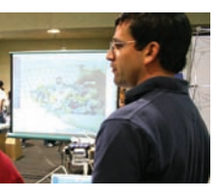
"Your presentation on 'Introduction to Science'… received high marks from everyone. They especially enjoyed the hands-on marshmallow and spaghetti molecular structure demonstration."

Educator reviewing the booth prepared by Scripps Research Professor Art Olson's lab for the Educational Technology Fair, attended by 2,500 San Diego middle and high school students.

"[This] really cool computer interaction with physical models… could show abstract properties like charge distribution and electrostatic fields with ease. These concepts are typically very difficult to visualize and explain to students, but the computer visualization made it really clear, and really simple."

Susan Shepard, biology teacher at Jupiter High School, Florida.

"Science Saturday was terrific and the students keep talking about it. Many thanks to all at Scripps who set up and ran the lab activities, answered questions about themselves and their research, and provided an eye-opening experience…"



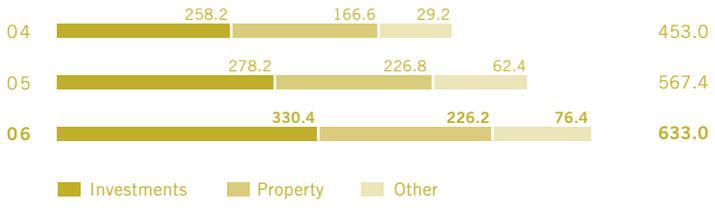
The Scripps Research education and outreach programs are made possible by many generous supporters. This year, the Biogen Idec Foundation made its first donation—$25,000 to fund San Diego teacher interns. Other supporters of the California programs include: the Maurice J. Masserini Charitable Trust (administered by Wells Fargo Bank), the Arthur Vining Davis Foundations, John and Susan Diekman, Ralph and Shirley Shapiro, the William Randolph Hearst Foundation, and Oliver and Norma James. The William R. Kenan, Jr. Charitable Trust funds the Florida programs.

Scripps Research Financial Highlights

FISCAL YEARS ENDING SEPTEMBER 30

Sponsored Programs
(millions)

Total Assets
(millions)



Net Assets
(millions)

Asset/Debt Ratio
(millions)

Net Income
(millions)

John J. Moores
Chair, Board of Trustees

Letter from the Board of Trustees Chair

Dear Friends:

As federal dollars from the National Institutes of Health and other government agencies diminish and become more restrictive, our donors become ever more important to our work. Your generosity has permitted the institute to continue to make significant progress in improving human health.

Philanthropy – The Year in Review

The Skaggs family continued their extraordinary commitment to the institution. The Skaggs Institute of Chemical Biology permits us to tackle the most complex research problems in innovative ways across disciplines and fields. The family also established the Skaggs Oxford Scholarships. Outstanding graduate students are spending time at both our Kellogg School of Science and Technology and Oxford before being awarded a joint Scripps/Oxford degree. It is the first joint degree offered by Oxford in its 800-year history.

Continuing generous gifts from Helen Dorris have helped the Harold L. Dorris Neurological Institute and the Helen L. Dorris Child and Adolescent Neuro-Psychiatric Disorder Institute on campus make significant strides in the study of schizophrenia, Alzheimer's disease, and other neurological disorders.

An ongoing financial commitment from Mark Pearson is helping our scientists combine the latest biomedical research with innovative clinical treatment to fight alcohol and drug addiction at the Pearson Center for Alcoholism and Addiction Research, established by an initial generous gift from Mark.

A new alliance between Scripps Research and McDonald's is fighting the critical and growing problems of childhood obesity and Type 2 diabetes among children. McDonald's is investing $2 million in the initial, two-year phase of an innovative research and public education partnership. This collaboration unites Scripps Research's world-renowned scientists, committed to groundbreaking research in pediatric health concerns, with McDonald's 50-year legacy of supporting programs that impact children's health, wellness, and everyday lives. Our shared hope and vision for this program is that it will lead to future generations of healthy adults in America.

Four years ago, we were honored to name our graduate program "The Kellogg School of Science and Technology" after our good friend, benefactor, and trustee emeritus Jean Kellogg and her late husband, Keith. In spite of its short history, the school is ranked among the top ten in the nation in biology and chemistry. This year, a bequest from Keith added $1.4 million in support of the school and institute.

A generous gift of $1 million was contributed this year by George and Patsy Conrades to provide unrestricted support to Scripps Florida. George, a fellow trustee, has been a long-time supporter of basic research and its role in providing American society with not only new knowledge, but also critical improvements in the welfare of its citizens.

Finally, an extremely generous new gift from the Alafi Family Foundation is supporting the pioneering and breakthrough biomedical research of the internationally renowned Dr. Charles Weissmann at Scripps Florida. The gift is providing hope to patients with serious, chronic, and life-threatening illnesses, such as malaria, tuberculosis, and prion disease, as well as their families.

While these gifts are significant, all gifts from the Scripps Research donor family—whatever the amount and whether they are unrestricted or directed—make our work possible. →

The Need for Unrestricted Gifts

Each of the above directed gifts are extremely important and integral to improving quality of health in a variety of different areas. Just as necessary are unrestricted gifts… the lifeblood of the institute.

With unrestricted gifts, Scripps Research has been able to both recruit internationally recognized new scientists to produce groundbreaking new disease research, and to support the education of outstanding young scientists at the Kellogg School of Science and Technology.

There is a word that appears repeatedly in scientific literature—serendipity. Coined by English writer Horace Waldpole in 1754, the term refers to the heroes of a fairy tale, "The Three Princes of Serendip," who wandered freely and were forever "making discoveries by accidents and sagacity of things they were not in quest of."

Modern science is a chronicle of serendipitous discovery.

Serendipity is not just dumb luck. Unpredictable results and unanticipated external factors are as much a part of scientific endeavor as cool reason, but only when strong intellect responds to an unexpected situation does serendipity work. It is axiomatic of basic scientific research—chance favors the prepared mind.

The Scripps Research Institute is a treasure trove of prepared minds, brilliant scientists whose discoveries can be limitless if their insight and perseverance are given the room to pursue unexpected leads.

Government Cutbacks and Restrictions – Our Challenge

It is becoming increasingly difficult for researchers to wander as freely as did the Princes of Serendip. Clearly, much effort must be directed towards solving immediate practical problems, but it is the unmapped routes of basic science research that often deliver us to the most remarkable destinations.

Annual funding by the National Institutes of Health has helped Scripps Research maintain its preeminent position. However, faced with growing budget pressures, Congress has cut overall government investment in scientific research by over $772 million for this year, making it harder for our researchers to secure federal dollars. The National Institutes of Health projects a decline in the number of research grants by over 400 for the second consecutive year.

Scripps Research depends on private philanthropists, like you, to enhance and extend its work in new, often nontraditional directions.

The Need for Personnel, Equipment, and Buildings

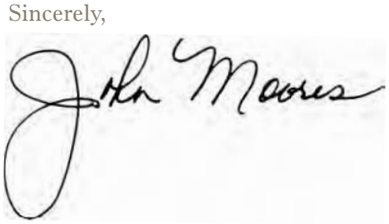
In addition to laboratory research—the heart of the institute's work—unrestricted gifts help cover costs of personnel and buildings which in other institutions, such as state universities, are subsidized by taxpayers. At Scripps Research, every unrestricted dollar supports research by insuring that scientists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

Thank You!

Throughout this report, you'll find compelling quotes from our donors as to why they have chosen to support Scripps Research with unrestricted gifts.

Your contributions – whatever the amount—are helping to improve the welfare of humankind. On behalf of the 3,000 staff in La Jolla and Florida, I thank you and applaud you.

Sincerely,



John J. Moores
Chair, Board of Trustees

Development Report

MAJOR DONORS TO THE SCRIPPS RESEARCH INSTITUTE

The Scripps Research Institute would like to thank its generous donors. Your support has helped fulfill the institute's mission to serve humanity by creating basic knowledge in the biosciences, by applying breakthroughs in research to the advancement of medicine, and by educating and training young scientists for biomedical research and its application to human welfare. Your contributions help build a foundation of knowledge that will have a profound impact on humankind for generations to come. On the following pages, we recognize the commitment of contributors who have opened their hearts and supported Scripps Research this year. We give special recognition in sidebars to a few of the people whose gifts demonstrate how private philanthropy advances the work of Scripps Research scientists.

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

SPECIAL ACKNOWLEDGEMENT FOR LIFETIME GIFTS

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

Anonymous (9)
Alafi Family Foundation/
Margaret Alafi, Ph.D.
The ALSAM Foundation/
Mr. and Mrs. L.S. Skaggs/
The Skaggs Institute for Research
American Cancer Society
American Heart Association
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Betty L. Springer-Baker†
Sam & Rose Stein Charitable Trusts†
Mrs. Frank E. Sugg†
Buddy Taub Foundation

JEAN KELLOGG

Such good work is done here.
I might not understand its scientific
aspects totally, but I understand
its importance.

THE SCRIPPS LEGACY SOCIETY

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

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Corinne E. Abel†
Shirley Ahrens
Eileen M. and John R. Anderson, IV
Kenneth and Ann Bacheller
Mike and Stella Banich
Alma Lee Barker†
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Mrs. Michael Buckley
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Melda I. Wilcox
Ms. Yvonne Wylie
John and Shirley Zeien

THE SCRIPPS COUNCIL OF 100

$100,000 and above

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Cystic Fibrosis Foundation
Cystinosis Research Foundation
Cytel Corporation
Charles A. Dana Foundation

MARGARET E. HASTINGS

I set up a designation with Scripps Research because I was so impressed with its reputation compared to other schools, as well as the reach and variety of the research.

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National Multiple Sclerosis Society
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ALEXANDER W. DREYFOOS

I was immediately impressed by the power of Scripps Research to attract great researchers, provide them with the stimulating environment of a beehive—not a bureaucracy—and give them the freedom and encouragement to pursue their work without interference.

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We have done our best to make this list an accurate reflection of gifts to Scripps Research from October 1, 2005 to September 30, 2006. If errors or omissions exist, please accept our apologies and call us at (858) 784-2037. Thank you, Scripps Research Development Staff.

I contribute to Scripps Research because its research mission is so terribly important to improving our health and that of future generations.

THOMAS E. DEWEY, Jr.

Opportunities for Giving

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

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

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

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

UNRESTRICTED GIVING

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

DISEASE RESEARCH PROGRAMS

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

THE CENTER FOR INTEGRATIVE MOLECULAR BIOSCIENCES

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

THE HAROLD L. DORRIS NEUROLOGICAL RESEARCH INSTITUTE

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

The center investigates a variety of neurological disorders, including *schizophrenia* and *Alzheimer's disease*, as well as increasing scientists' understanding of the aging process in the brain. The center has attracted an international team of brain specialists, led by Tamas Bartfai, Ph.D., former head of central nervous system research at Hoffman-LaRoche (a pharmaceutical company in Basel, Switzerland) and former chairman of the department of neurochemistry and neurotoxicity at Sweden's Stockholm University.

Naming Opportunities

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

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

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

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

Giving O pportunities

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

THE INSTITUTE FOR CHILDHOOD AND NEGLECTED DISEASES

For a number of years, researchers have attempted to use gene therapy and other treatments against *cystic fibrosis, muscular dystrophy, childhood deafness*, and certain forms of *cancer*. Although none of these efforts has led to consistent success, collectively they have laid the groundwork for more successful approaches. In other cases, such as *autism*, scientists are only now uncovering genetic clues that may lead to better treatments. The majority of the world's population lives in developing countries where parasitic diseases such as *malaria* and *river blindness* remain pandemic. The institute uses the latest advances in biology to target therapies for these persistent problems.

Naming Opportunities

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

THE PEARSON CENTER FOR ALCOHOLISM AND ADDICTION RESEARCH

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

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

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

COMMUNITY HEALTH EDUCATION

As part of its new national platform, Scripps Research has established the Center for Translational and Community Medicine in La Jolla, under the leadership of Richard A. Lerner, M.D., the institute's president, and the direction of Katja Van Herle, M.D., M.S.P.H., professor of medicine and director of community health education.

The center aims to increase Americans' awareness of growing health problems—such as the critical connection between obesity, diabetes, and cardiovascular disease—and to translate advances in basic research into improved clinical practice.

The center's work includes: 1) educational projects in collaboration with individuals, foundations, and corporations to improve Americans' health understanding and behavior from a solid scientific basis; 2) special centers, funded by philanthropy, to advance clinically directed research in disease areas of interest to donors; and 3) worldwide referral and connection to the best medical specialists in any area of diagnosis or therapy, based on individual and family consultations and preparatory conferral by Dr. Van Herle with physicians and other health professionals who will be involved in the patient's care.

Giving Opportunities

Additional funding would facilitate: 1) the hiring of experts in public health education to reach out to additional communities, especially in underserved areas both locally and across the country; 2) an expanded education program on health-related subjects in Scripps Research scientists' areas of expertise; and 3) the development of computer programs and other material for children, the elderly, and underserved populations.

ENDOWMENT

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

Naming Opportunities

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

SCHOLARSHIPS AND FELLOWSHIPS

THE KELLOGG SCHOOL OF SCIENCE AND TECHNOLOGY

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

In 1989, Scripps Research established a Ph.D. program in mac-

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

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

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

INTERNSHIPS

HIGH SCHOOL STUDENT RESEARCH EDUCATION PROGRAM

Scripps Research's High School Student Research Education Program exposes students to basic biomedical research, provides hands-on laboratory experience, and motivates young people—particularly those students whose groups are historically underrepresented—to continue their education in the sciences at this impressionable age. Students participate in spring enrichment tutorials in molecular biology and chemistry, a summer research internship program in a research laboratory, and a mentoring program with a Kellogg School graduate student who guides them through SAT test preparation, college selection, the application essay, and financial aid search.

SUMMER RESEARCH INTERNSHIP PROGRAM FOR TEACHERS

Study after study has found that American schools fall short in helping students achieve scientific literacy. A critical element in improving science education is effective teacher training. Scripps Research's Middle/High School Science Teacher Summer Research Program exposes teachers to new laboratory techniques and procedures, informs them about contemporary issues in biomedical research, and forges long-lasting ties between secondary school educators and Scripps Research scientists. The program emphasizes the scientific process, research planning, bench experience, experimental design, data analysis, and interaction with laboratory personnel. In addition to an intensive, hands-on, eight-week summer experience, teachers are expected to use the laboratory experience as a springboard to create and enhance their curriculum and to become resources for other educators.

UNDERGRADUATE SUMMER RESEARCH INTERNSHIP PROGRAM

Scripps Research's Undergraduate Summer Research Internship Program is an intensive eight-week research experience for talented undergraduate students currently studying biology, chemistry, mathematics, physics, computer science, cognitive science, or neuroscience. The program exposes students to basic biomedical research, provides hands-on laboratory experience, and encourages them to continue their education in the sciences. The program is also committed to increasing the number of students drawn from communities historically underrepresented in the sciences.

Giving Opportunities

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

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

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

BUILDINGS AND LABORATORIES

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

In Florida, a gift of $10 million will name one of three new buildings under construction on land provided by Palm Beach County. In California, a gift of $8 million will name the immunology building.

BUILDINGS AND LABORATORIES

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

Scripps Research enjoys one of the world's leading private computational capabilities, with an array of computers. Research is also supported by x-ray crystallography laboratories, high performance NMR spectrometry including state-of-the-art 900 and 750 MHz instruments, electron microscopy, optical spectroscopy, a centralized DNA sequencing laboratory, and a fluorescence-activated cell-sorting facility.

Scripps Research scientists require state-of-the-art facilities and equipment to remain on the cutting edge of research and rapidly advancing technology. New laboratory equipment is continually being developed to improve the efficiency and effectiveness of basic research, and new technology provides ever-shorter paths from discoveries to their application in prediction, diagnosis, and treatment of disease. Gifts of discretionary funding are critically important to support the ongoing modernization of laboratories.

IMMUNOLOGY DEPARTMENT

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

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

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

Other Naming Opportunities

Other naming opportunities in the immunology building include the following:

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

Ways to Give

GIFTS OF CASH, CHECKS, OR CREDIT CARDS

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

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

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

GIFTS OF STOCK

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

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

NAMING GIFTS

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

To discuss these opportunities, please call the major gifts office at (858) 784-9365. In Florida, please call the office of external affairs at (561) 656-6401.

GIFTS IN MEMORY OR CELEBRATION

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

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

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

CORPORATE GIFTS

Gifts from businesses and corporations continue to pay dividends by fostering the spirit of independence, innovation, and entrepreneurship that has characterized Scripps Research since its founding. Companies and their executives become involved in the institution's work as donors, as event sponsors, and at special recognition events. Many companies encourage philanthropic giving by their employees and match an employee's gift with a corporate contribution.

Donors interested in this opportunity should obtain the necessary matching gift form from their employer (usually the human resources office), complete it, then mail it to:

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

Many companies also find that association with scientific, educational, or public events presented by The Scripps Research Institute provides a ready-made way to reach intelligent, motivated

customers, reward clients and employees, and create community good will.

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

To discuss ways in which your company can enjoy the dividends of being a donor or a sponsor, please call (858) 784-9367.

FOUNDATION GIFTS

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

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

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

ALUMNI GIFTS

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

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

BEQUESTS

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

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

The following is an example of an unrestricted bequest provision: "I give [insert dollar amount, property to be given, percentage of the estate, or 'the remainder of my estate'] to The Scripps Research Institute, a nonprofit corporation, tax identification number 33-0435954, headquartered at 10550 North Torrey Pines Road, La Jolla, California 92037, for its general use and purposes."

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

GIFTS THAT PAY INCOME FOR LIFE

Charitable Gift Annuity

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

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

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

Charitable Remainder Trust

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

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

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

REAL ESTATE

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

Real estate is not limited to personal residences. It includes investment or commercial properties, agricultural properties, parcels of land, and more. All offer varying advantages, depending on whether you own the property outright or share ownership, and how much the property has appreciated. You can choose to

give 100 percent or a percentage of the property to the institute. You also can choose to donate any tangible personal property inside the building as a separate gift.

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

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

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

LIFE INSURANCE

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

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

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

GIFTS OF RESIDENCE WITH LIFE ESTATE RETAINED

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

Life Estate Agreement

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

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

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

Life Estate Agreement with Gift Annuity

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

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

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

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

CHARITABLE LEAD TRUST

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

Charitable Lead Trust Plans

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

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

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

Recognizing Our Donors

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

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

THE SCRIPPS COUNCIL OF 100

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

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

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

To learn more about The Scripps Council of 100, please contact Denise M. Scalzo, vice president of development, at (858) 784-9365, (800) 788-4931, or *scalzo@scripps.edu*.

1,000 FRIENDS OF SCIENCE

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

Members receive the following:

— An annual report outlining the impact of the member's gift,

— An invitation for two to the annual 1,000 Friends of Science event, held on campus in California,

— Invitations and reserved seating for lectures and receptions called *Frontiers in Science* (in California) and *Frontiers in Scripps Science* (in Florida),

— *Endeavor*, Scripps Research's magazine, and *Scripps Discovers*, a quarterly newsletter for donors.

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

Founders' Circle:	/ $5,000 - $9,999
President's Circle:	/ $10,000 - $24,999
Chairman's Circle:	/ $25,000 - $49,999
Fellows' Circle:	/ $50,000 - $99,999

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

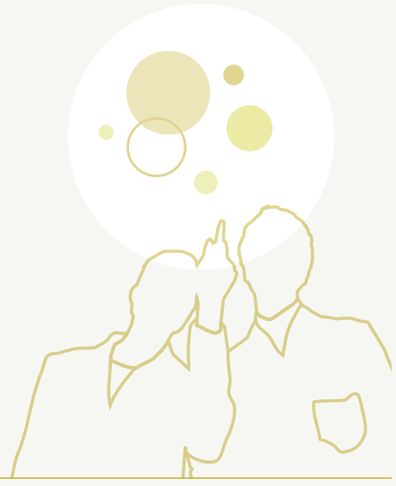
To learn about opportunities for special gifts restricted for a particular disease, research area, or fellowships and scholarships, please contact Roz Hodgins, development officer for foundations and major gifts, at (858) 784-8274 or *hodgins@scripps.edu*.

THE SCRIPPS LEGACY SOCIETY

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

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

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



"Scripps Research is really a unique place in the collegiality of its faculty and in the willingness of faculty to cross specialized niches in order to undertake interdisciplinary research. The scientific environment promotes collaboration, allowing us to tackle big problems in creative ways."

ERIC ZORRILLA, PH.D.

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