

SCRIPPS DISCOVERS

Accelerating Discoveries, Saving Lives

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INSTITUTE UPDATE

Scripps Research Celebrates 16th Commencement

> In May, The Scripps Research Institute celebrated its commitment to excellence in education and research with its 16th commencement.



The commencement graduated 28 Ph.D. candidates and recognized Scripps Research trustee Claudia S. Luttrell with an honorary degree. Distinguished scientist Ernest Beutler, chair of the Department of Molecular and Experimental Medicine, delivered an inspiring keynote address.

The official ceremonies began with a winding march across the oceanside campus in the fresh morning air. Led by Scripps Research President Richard Lerner, the regal procession included not only Kellogg School of Science

continued on page 2

Scripps Research trustee Claudia S. Luttrell was recognized with an honorary degree at the 16th commencement by Associate Deans of Graduate Studies Stephen Mayfield and Jamie Williamson, and Dean of Graduate Studies Jeffery Kelly.

Inside:

- 3... Innovative Method to Produce Highly Sought-After Drug
- 4... Scientist Profile: Brunhilde Felding-Habermann
- 6... Donor Profile: Patti and Stanley Silver
- 6... Hanneken Receives Grant for Eye Disease Research
- 7... Three Scientists Elected to National Academy of Sciences

BACK COVER:
Partners, Contact Us

Scripps Research Again Receives Four Stars from Charity Navitagor



> The Scripps Research Institute has again received a coveted four-star rating from Charity Navigator, the internet rating service that evaluates the efficiency and financial accountability of nonprofit groups. This is the seventh consecutive four-star rating for Scripps Research.

“Less than 1 percent of the charities we’ve rated have received at least seven consecutive four-star evaluations, indicating that The Scripps Research Institute outperforms most charities in America in its efforts to operate in the most fiscally responsible way,” wrote the organization’s interim president/chief operating officer, Michael Smith.

continued on page 2

and Technology deans, honorary degree recipient, faculty advisors, and graduating students, but also fellow Kellogg School students and faculty members.

After the group arrived at the Neurosciences Institute Auditorium filled with the friends, family, and supporters of the graduating students, Lerner offered welcoming remarks and Professor Jeffery Kelly, dean of graduate studies, spoke on some of the factors making the Kellogg School exceptional.

Kelly noted that, from its inception, the Scripps Research program was able to attract the very best students because of the power of its mission—to train the next generation of scientists as individuals capable of bringing together the principles of various scientific disciplines, in Kelly's words, "the skill set required to solve the complex problems of today and especially tomorrow."

"Innovation is the hallmark of this program," Kelly said.

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

published in *The Chronicle of Higher Education* ranks the Kellogg School as best in the nation in biophysics, as well as second in immunology and seventh in biochemistry.

The Kellogg School, which first opened its doors on the La Jolla, California, campus in 1989, currently trains about 225 doctoral students, who attend classes, complete lab rotations, and write a dissertation that offers an original contribution to their field.

The school can now boast of more than 300 accomplished alumni, including the 2008 graduates. Three of these alumni—two from this year's graduating class—conducted studies on the Scripps Florida campus, which accepted its first transfer students in 2005 and began accepting entering students in 2006.

"Our reputation as a first-rate research institute has significant meaning because of the remarkable quality of our faculty and the resources we make available to our students," said William R. Roush, associate dean for the Scripps Florida graduate school program, as well as professor of chemistry and executive director of medicinal chemistry at Scripps Florida, commenting before the ceremony but

echoing Kelly's remarks. "This is a community of scholars, a place where there are no barriers to doing groundbreaking research."

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

Beutler—an eminent scientist who has published more than 1,000 scientific papers, written more than 10 books, and made a host of discoveries, including X-inactivation, and novel treatments for Gaucher disease and several forms of leukemia—addressed the graduating students and others in the auditorium, speaking to the joys of a career in science, as well as its responsibilities.

After Beutler concluded his remarks, congratulating the students and their families, each student was honored individually. Ph.D. advisors stepped up to the stage one by one to speak about each graduate's array of scientific and personal accomplishments. It was a talented crowd.

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

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

continued on next page

Four Stars, CONTINUED

"This 'exceptional' rating from Charity Navigator differentiates The Scripps Research Institute from its peers and proves that it's worthy of the public's trust." Organizations are evaluated on quantifiable criteria, including the ratio of fundraising costs to results and income growth.

"We're delighted that Scripps Research is again being recognized as an outstanding organization," said Wendy Scott Keeney, Vice President of Philanthropy at Scripps Research. "Gifts to the institute support excellence and innovation in research, both in basic science and in the prevention, diagnosis, and treatment of human disease."

Team Devises Innovative Method to Produce Highly Sought-After Drug

> A team of Scripps Research Institute scientists has developed an inexpensive and in many ways astonishing new method for economically producing a promising pharmaceutical steroid.

The molecule, called cortistatin A, which was isolated in 2006 from a marine sponge discovered over 100 years ago, has shown huge promise for treating conditions ranging from macular degeneration to cancer.

This achievement led by Scripps Research chemist Phil Baran, Ph.D., and reported in an advanced, online issue of the *Journal of the American Chemical Society*, marks the finish line in a race that saw numerous research laboratories working to accomplish the feat. As with all potential pharmaceuticals, an efficient and economic means of

producing cortistatin A is needed to enable research into the drug's effectiveness as a disease treatment, as well as to open the possibility of eventual commercial production.

"It's nice to see that a potentially huge application exists for science that was developed with the sole intention of conducting basic research at the core of organic chemistry," says Baran.

At least 20 other research groups around the world have been developing methods for synthesizing cortistatin A, in part because it has shown strong pharmaceutical potential, but also because its structure is especially challenging to recreate.

From the outset, Baran and his team decided that modifying the commonly available steroid prednisone, which has certain similarities to cortistatin A, would be the best

continued on page 4

Commencement, CONTINUED

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

The commencement ceremony culminated in the granting of an honorary degree to Claudia Skaggs Luttrell, whose achievements include promoting scientific collaboration in her capacity as a member of the Scripps Research Board of Trustees, president of the Skaggs Institute for Research at Scripps Research, and chair of the Skaggs Oxford Scholarship Program, a joint academic training program at Scripps Research and Oxford University.

"It's an honor to recognize [Claudia Skaggs Luttrell] and what a special role her distinguished family has played," Lerner noted. "This program would not be what it is today without the generous support of the Skaggs family."

Kelly agreed, noting that the Skaggs family's "extraordinarily generous" gift of \$100 million in 1996 helped transform Scripps Research into

one of the leading biomedical research centers in the world.

After accepting her degree, Luttrell stepped up to the microphone to deliver some brief remarks that paid tribute to her father, Sam Skaggs, and reiterated her commitment to continuing his legacy and vision. Luttrell noted that her father was "one of the giants of corporate America," who took over the family business, an 11-store chain of drug stores, at the age of 26. Before his retirement in 1995, he had pioneered the first successful combination food and drug store—"literally changing the way Americans shop"—and built the company into one with more than 1,700 stores in 26 states and annual revenues of \$22.2 billion. Luttrell noted that his record of philanthropy is also extensive.

"My father's philosophy is grounded in a strong belief that basic biomedical science should translate into new medicines to treat disease, new

diagnostic tests, and new methods to prevent disease," Luttrell said. "This remarkable institute fulfills this philosophy by training the next generation of scientists, while at the same time contributing to the scientific knowledge base that in turn leads to new discoveries for drug targets and new biological markers for disease."

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

Her words were greeted by a warm and enthusiastic reception.



Dr. Phil Baran

route for synthesis. Baran says prednisone, commonly used as an immunosuppressive drug and to treat inflammation associated with allergies, was attractive not only because it is inexpensive and readily available. He also liked the idea of transforming one of the most abundant steroids on the planet, which was discovered on land, into an exceedingly rare marine-derived steroid.

The team accomplished the remarkable transformation from prednisone to cortistatin-A in just 15 steps. Though this may sound complex, it is exceedingly simple in relative terms for a field in which 30 or more expensive, complex steps are sometimes used to create commercially available drugs. The technique yields a healthy three grams of cortistatin-A from every 100 grams of prednisone, and Baran believes that optimization triple this efficiency will be possible.

“The whole point of this was to study fundamental organic chemistry and really provide some innovative new methods,” says Baran, a goal the team has clearly accomplished.

At one intermediate step in the prednisone transformation, by forcing the molecule to reversibly bond with itself at certain points, the researchers were able to achieve a critical reaction that makes the later steps yielding cortistatin-A possible. “It has a contorted form at that point that doesn’t bear a lot of resemblance to the final product, but the molecule is literally protecting itself,” Baran notes.

That protection is a key point, because complex chemical syntheses normally demand the addition of extra molecules called protecting groups that bond to and protect certain sections of the molecule being synthesized from reacting in undesirable ways. This adds not only complexity and time, but also cost to the production of a drug.

Causing the intermediate molecule in the cortistatin-A to protect itself is one way Baran avoided the overuse of protecting groups, allowing him to resort only minimally to this technique in the synthesis.

A cascade of reactions follows the self-protection trick, leading to an intermediate molecule that is just one change away from cortistatin A. The overall synthesis culminates with a precisely targeted conversion of a single hydrocarbon

bond on that late intermediate molecule that manages to leave a number of vulnerable components unchanged. This was achieved through the careful selection of chemical reagents and solvents added in a way that exploits slower reaction times with those vulnerable components so that the necessary conversion is done before any unwanted reactions occur. “That part of the synthesis is unique and counterintuitive,” says Baran.

Baran is currently focusing on further exploration of related chemistry. The methods he and his team devised for the new synthesis may aid in the development of production methods for a host of other steroids, but Baran is most interested in creating new molecules similar to cortistatin-A, or analogs, that may show useful new biological activity for potential development into new drugs.

Baran says producing a library of analogs should now be relatively straightforward, because one of the intermediate steps in the cortistatin-A synthesis, dubbed cortistatinone, is especially amenable to the addition of a huge range of chemical components. Each such addition could lead to its own pharmaceutically interesting activity. “Adding those other pieces,” says Baran, “will be just like putting Legos® together.”

The paper is dedicated to Harvard University Professor and Nobel laureate E. J. Corey on the occasion of his 80th birthday.

SCIENTIST PROFILE

Brunhilde Felding-Habermann: Interfering with the Spread of Breast Cancer and Melanoma

Breast cancer and melanoma have a propensity to metastasize and when they do, they can be deadly.

Metastasis is a dangerous phenomenon in which cancer cells separate from a tumor mass, move through the bloodstream, anchor down in a distant tissue or organ, and begin a new cancer that might compromise the function of that organ. While surgeons can remove cancerous tissue, such procedures are greatly complicated if a tumor spreads to other organs. Although science and medicine have made tremendous strides in early detection and successful treatment, breast cancer and melanoma, the deadliest type of skin cancer, still claim tens of thousands of lives a year—usually the end result of metastasis.

What leads tumor cells to metastasize? What determines where the metastatic cells go? Why do breast cancers

continued on next page



Dr. Brunhilde Felding-Habermann

typically metastasize and form satellite tumors in the brain, lungs, liver, and bones? What is it about the vascular cells in these tissues that interacts with circulating breast cancer cells and allows them to invade, forming a new tumor?

Scripps Research Associate Professor Brunhilde Felding-Habermann, Ph.D., who works on metastatic melanoma and breast cancer cells, is working to find answers to these questions.

“Too many patients still die from metastatic breast cancer and melanoma,” said Brunhilde. “What we are trying to find out is what determines whether or not breast cancer or melanoma cells will metastasize. Our goal is to develop new therapies that can eliminate the spread of cancer, especially to the brain.”

Cancer is a complicated disease. It can be caused by subtle mutations within normal cells. After certain mutations occur, a cancer cell grows resistant to normal programmed cell death, dividing out of control, over and over, and forming a solid tumor. Also common to tumor cells are mutations that lead them to metastasize and spread to distant organs.

Brunhilde and her group have found a way to inhibit the attachment of disseminating tumor cells and

inhibit the metastatic ability of breast cancer cells with special antibodies. She has teamed up with Scripps Research Professor Kim Janda, Ph.D., who has generated a combinatorial antibody library from blood samples from numerous cancer patients, in order to isolate antibodies that are present in the blood of cancer patients and recognize metastatic tumor cells. Brunhilde and her team have found antibodies in the immune repertoire of cancer patients that target the tumor cells.

“Our work has shown that cancer patients can produce antibodies that may very actively interfere with metastasis. We found antibodies that block the ability of human breast cancer cells to metastasize and help extinguish breast cancer that had already spread.”

— Dr. Brunhilde Felding-Habermann

“Optimizing these antibodies, we might be able to develop powerful anticancer drugs that can inhibit cancer spreading. I think we’re moving in the right direction.”

This finding is highly significant because of the potential of using such

antibodies as a new way to treat cancer. Despite recent progress in cancer therapy, no treatment is known today that prevents cancer spreading.

“One great thing I appreciate here at Scripps Research is that you can have very exciting collaborations merging biology with chemistry, such as this one with Dr. Janda. The work in my lab has really benefited from all of these interactions. In addition to my faculty colleagues, the young researchers who come to Scripps Research for their post doctoral studies are so very, very gifted—it’s difficult to find good people like these who work so hard and are driven to fight disease developing their own scientific careers.”

“I also find you really have the freedom to explore ideas here,” said Brunhilde, who left Scripps Research for a few years and established a research lab in a pharmaceutical company before coming back. “This freedom in research is very important to developing new concepts that can lead to innovative therapies.”

Brunhilde’s laboratory has discovered a molecule critical for the spread of melanoma. In another collaboration with Scripps Research Professor Dale Boger, Ph.D., the team is screening inhibitors against this molecule to find a new treatment for metastatic melanoma.

Brunhilde is also collaborating with Scripps Research Professor Eric Topol, an expert in genomics, in examining the genes of healthy senior citizens and how these genes may have protected them against cancer while others are afflicted. The study involves examining how a good immune system can stop someone from developing cancer with the goal being to “fish out” the best antibodies which might be used as future cancer treatments.

continued on page 6

Brunhilde's research on cancer metastasis to the brain is fairly unique among researchers across the country. "It's difficult to conduct experiments on brain metastasis and there are no therapies out there, yet the need is so great—even a little progress could lead to a breakthrough" she said. "We're making progress here though a close collaboration with neurosurgeons at UCSD who have made metastatic brain lesions available for our study."

Brunhilde recently hosted a group of breast cancer advocates from the National Breast Cancer Coalition Fund (NBCCF). NBCCF has spearheaded a major increase in federal funding for breast cancer research. They came to Brunhilde's lab to see her significant research firsthand.

"The visit was a great success," said Brunhilde. "It not only raised the profile of Scripps Research among advocates, but it also gave my lab a big boost in motivation to hear what breast cancer survivors hope to see accomplished in breast cancer research. It brought home why we're doing this research."

Brunhilde came to Scripps Research in 1993 after receiving her Ph.D. from Phillips University in Germany. "It has been a labor of love," she said. "The research has really allowed me to express myself and make a difference."

Hanneken Receives Pfeiffer Grant for Eye Disease Research

Associate Professor Anne Hanneken, M.D., recently received a grant from the Gustavus and Louise Pfeiffer Foundation, an organization that supports the advancement of medicine and pharmacy, including scientific research, post-graduate scholarship and fellowship assistance, and studies in nutrition, blindness, deafness and other physical disabilities. The award to Hanneken will fund research on the ability of flavonoids to prevent oxidative stress and cell death in the retina, with the long-term goal of developing preventive therapies for people at high risk for macular degeneration and blindness.

In addition to this award, the Pfeiffer Foundation is supporting three graduate student fellowships in the coming year.

DONOR PROFILE

Patti and Stanley Silver: Improving Health Awareness through Philanthropy

Patti Silver of Beverly Hills became a patient of Katja Van Herle, M.D., M.S.P.H., nine years ago and it has been a love affair ever since. During these years, Patti has undergone both a brain tumor and diabetes, and has become very close to Katja.

Katja maintains a clinical practice in Los Angeles, while serving as the Director of Scripps Research's Community Outreach for Research and Education (CORE) in La Jolla. The CORE program, which is national in nature, is increasing Americans' awareness of growing public health problems such as the critical connection between obesity, diabetes and cardiovascular disease. It is working in collaboration with foundations and corporations, like McDonald's, to improve Americans' health understanding and behavior.

"Katja's way is kind and very caring. She is the best," said Patti. "We talk about everything—she threatens me on my nutrition—sometimes she's even my psychologist!"

"I knew that Katja needed support for the CORE program and I would do anything for her," said Patti. She and her husband Stanley have now provided five generous gifts over the past five years to support the CORE program.

Additionally, the Silvers have helped fund the research of Donald Becker, the UCLA neurosurgeon who successfully performed Patti's 13.5 hour benign brain tumor operation.

Patti was raised in a philanthropic environment. She's the daughter of the late Chicago businessman, art collector and philanthropist Leo S. Guthman, a plastics manufacturer who developed coating for the inside of beer cans, among other things. The Guthman Fund has supported numerous charities.

Patti is a businesswoman in her own right. Since 1970, she has owned a shoe boutique, Fred Segal Feet, on Melrose Avenue in Los Angeles. Stanley, who is now retired, helps Patti in the endeavor.

Outside of work, Patti serves on the acquisition committee for modern art at the Los Angeles County Museum of Art and is on the board of governors at Cedars-Sinai Medical Center. The Silver's have a passion for art and have an extensive collection. Some of their favorites are works of Ad Reinhardt, Alexander Archipenko, Henry Moore, Lynn Chadwick, Jean Arp, and Picasso. They even have eclectic collections of giraffes, tea pots, and old 17th and 18th century snuff boxes. They introduce pieces around their home like old friends, without a hint of pretension.

Stanley even has a batting cage, where he practices every day after working out on his treadmill. "I'm a frustrated hitter and could not hit a curve ball so I became a pitcher and had a tryout with the Philadelphia Athletics, but decided to go to the University of Colorado on a baseball scholarship." Stanley's love of baseball carries over to his collection of 1,200 autographed baseballs. All were gifts from players, friends, or his father. He also has an extensive collection of World Series and All Star Game programs.

The Silver's are the happy parents of three children and have eight grandchildren. In addition to their art and baseball avocations, they love to travel.

Three Scripps Research Scientists Elected to National Academy of Sciences

> Three members of The Scripps Research Institute faculty were elected to the U.S. National Academy of Sciences this spring. Scripps Research is the only independent research institution in the nation to have three faculty members chosen this year.

The newly elected members are Bruce Beutler, Michael B.A. Oldstone, and Peter Wright. With this election, the number of National Academy of Sciences members currently working at Scripps Research stands at 19.

Created in 1863, the National Academy of Sciences is a society of world-renowned scholars in scientific and engineering research. Election to the academy is considered one of the highest honors that can be accorded a scientist or engineer.

"It's both a great honor for Scripps Research and an indicator of the unique quality of the institute's science that an organization of our size should have three faculty members elected to the nation's most prestigious scientific society in the same year," said Scripps Research President Richard A. Lerner. "On behalf of our Board of Trustees, the faculty, and everyone at Scripps Research, I congratulate Bruce, Mike, and Peter."

Bruce Beutler is the second in his family to be elected to the National Academy of Sciences. He joins his father, Ernest Beutler, chair of the Scripps Research Department of Molecular and Experimental Medicine and a member of The Skaggs Institute for Chemical Biology, who was elected to the academy in 1976.



Bruce Beutler, M.D., is chair of the Department of Genetics at Scripps Research. His research focuses on the search for genes that are

required for normal immune function using the techniques of germline mutagenesis and positional cloning. In terms of output, the mutagenesis effort now underway in the Beutler laboratory is the largest in the world, and the only one primarily devoted to deciphering innate immunity. The long-range goal of the laboratory is to identify the key genes required for resistance to infection and to determine how they interact with one another.



Michael B.A. Oldstone, M.D., is a professor in the Scripps Research Department of Immunology and Microbial Science where he heads a laboratory of viral-immunobiology, and is an adjunct professor in the Scripps Florida Department of Infectology. His laboratory studies the nature and consequences of virus-host interactions. His studies focus primarily on negative-stranded RNA viruses, lymphocytic choriomeningitis virus (LCMV), and measles virus, as well as infectious folding protein disease (prions). Oldstone changed the once-accepted dogma that virus that persists in the body causes tolerance of the immune system, showing that both persistent LCMV and retroviruses elicit humoral B cell responses that lead to immune complex formation and disease of the kidney and blood vessels; he also extended these findings to human infections. Oldstone defined both LCMV and measles virus infection of lymphocytes and dendritic cells leading to suppression of the

immune system, findings also extended to human infections. He recently described a host immunosuppressive molecule induced by an infecting virus that leads to suppression of immune T cells; blockade of the molecule with antibody leads to resurrection of immune function and removal of the virus.



Peter Wright, Ph.D., is chair of the Department of Molecular Biology, Cecil H. and Ida M. Green Investigator in Medical Research, and member of the Skaggs Institute for Chemical Biology at Scripps Research. His laboratory has helped pioneer the use of high-resolution, multi-dimensional, hetero-nuclear magnetic resonance (NMR) spectroscopy to study protein dynamics, folding, and recognition, particularly the structures of protein-DNA and protein-protein complexes involved in the regulation of DNA-RNA transcription. These studies have provided new insights into the fundamental mechanisms of protein folding, which is closely linked to proper protein function. In addition, his use of multi-dimensional NMR spectroscopy has proven to be a powerful method for characterizing the structure and dynamics of unfolded protein states and protein folding intermediates.

Other National Academy of Science members currently at The Scripps Research Institute are Ernest Beutler, Floyd Bloom, Francis Chisari, Gerald Edelman, Albert Eschenmoser, Gerald Joyce, Richard Lerner, K.C. Nicolaou, Julius Rebek, Paul Schimmel, Peter Schultz, K. Barry Sharpless, Peter Vogt, Charles Weissmann, Chi-Huey Wong, and Kurt Wuthrich.

Partners

1 Scripps Florida's Education and Outreach Programs recently participated in a Community Health Fair with the T. Leroy Jefferson Medical Society at Dr. Mary McLeod Bethune Elementary School in Riviera Beach, Florida. **Kelly McAteer**, Scripps Florida Environmental, Health & Safety team member, leads a mother and son through a fun, drug discovery exercise designed to illustrate the identification of a possible cancer therapeutic. (upper left photo)



2 A group of over 125 members of Eastpointe Country Club turned out to enjoy an evening presentation and update on Scripps Florida by Barbara Suflas Noble, Scripps Florida director of external affairs. Attending the event were (right to left) **Monroe Potash**, chairman of Eastpointe's Community and Cultural Committee; **Sandy Mast**, Eastpointe membership director; and **Murray Green**, committee past-chairman. (upper right photo)



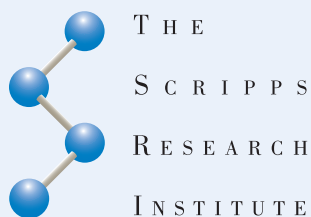
3 The Fraternal Order of Eagles, Ft. Lauderdale #3140, dedicated their April 2008 activities and events to support Alzheimer's research via The Unforgettable Fund. The Unforgettable Fund has supported Alzheimer's research at Scripps Florida since 2006. **Dr. Claes Wahlestedt**, Scripps Florida Professor of Biochemistry and Director of Central Nervous System Discovery (right), joins **Patty Doherty** of The



Unforgettable Fund (center), as she accepts a check for over \$5,000 from FOE #3140 members. (lower left photo)

4 In celebration of the fourth annual gathering of The Scripps Legacy Society this spring, Scripps Research planned giving donors and Kellogg School of Science and Technology students enjoyed a luncheon at the Beckman Center for Chemical Sciences atrium.

The Scripps Legacy Society is comprised of individuals who have included Scripps Research as a beneficiary in their estate plans. Ben Morris, vice president of facilities services, and Dr. Philip LoGrasso, associate professor and senior director for drug discovery at Scripps Florida, spoke about the progress of the new campus in Florida. Pictured here is Scripps Legacy Society member **Yvonne Wylie**. (lower right photo)



Contact Us: For more information about Scripps Research, visit our web page at www.scripps.edu/philanthropy

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