



SCRIPPS DISCOVERS

Improving Lives Through Research

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INSTITUTE UPDATE

Scripps Research Again Receives Four Stars from Charity Navigator



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

This is the sixth consecutive four-star rating for Scripps Research.

“Less than 12 percent of the charities we’ve rated have received at least two 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 executive director, Trent Stamp.

“This ‘exceptional’ rating from Charity Navigator differentiates The Scripps Research Institute from its

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RESEARCH UPDATE

Scripps Florida Campus Dedicated

> The Scripps Research Institute officially dedicated its Scripps Florida campus in Jupiter on March 9th to “increasing human knowledge, advancing biomedical science, educating the researchers of the future, and improving the health of humanity.”

At a ceremony before some 400 Scripps Florida employees and guests at the construction site on Florida Atlantic University’s (FAU) Jupiter campus, Scripps Research President Richard A. Lerner, M.D., thanked the people and leaders of Palm Beach County and the State of Florida for their contribution toward the establishment of Scripps Florida.

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Posing with the rendering of Scripps Florida’s new home in Palm Beach County are Marshall Criser, Retired Chair of the Scripps Florida Funding Corporation; Scripps Research President Richard A. Lerner, M.D.; John J. Moores, Chair of the Scripps Research Board of Trustees; Palm Beach County Commission Chair Addie Greene; former Florida Governor Jeb Bush; and Florida Governor Charlie Crist.

“We are honored to have with us today to share in this celebration Palm Beach County Commission Chair Addie Greene, former Governor Jeb Bush, and Governor Charlie Crist,” Lerner said. “Each has been instrumental in bringing Scripps Florida to where it is today and contributing to its future positive impact on the community, science, and human health.”

Construction on the first phase of Scripps Florida — three buildings totaling 350,000 square feet of laboratory and administrative space — is expected to be ready for occupancy in early 2009. Some 200 researchers, technicians, and administrative staff are currently at work in two buildings and several trailers adjacent to the construction site. The buildings will be turned over to FAU when the new permanent facilities open.

Former Governor Bush was eloquent in asking fellow Floridians to step forward with financial support for Scripps Research’s new venture in Palm Beach County. Turning to the television cameras, he said, “I’m not just talking to the audience with us today, but to all Floridians. So many of us have been successful financially, and we really need your help to fulfill the potential we set in motion here today. I got a message from Patty Doherty, whose brother is ill with cancer, and if

you’re listening, Patty, you’re the one who inspired me to make my plea for gifts to Scripps Florida research.”

After remarks from Commission Chair Greene and Governor Crist, John J. Moores, chair of the Scripps Research Institute Board of Trustees, made the formal dedication.

“On behalf of the Board of Trustees, faculty, employees, and friends of The Scripps Research Institute, we dedicate the Scripps Florida campus to increasing human knowledge, advancing biomedical science, educating the researchers of the future, and improving the health of humanity,” he said.

Marshall Criser, former chair of the Scripps Florida Funding Corporation that oversees the allocation of \$310 million of state funding, was recognized for his steady leadership during the first three years of Scripps Florida’s development.

The expansion of the Institute in Florida was spearheaded by then Governor Bush, and originally announced by President Lerner and Bush in October 2003. In November 2003, Governor Bush signed into law the historic piece of legislation that laid the groundwork for the expansion.

Initial plans called for construction on a parcel of land made available by Palm Beach County in the western

part of the county, but legal and other issues caused the county to decide a year ago to situate the facilities on 40 acres of the FAU campus and ultimately on an adjacent 100-acre property.

Scripps Florida, which will employ a minimum of 545 staff by the end of its state funding, is focused on the discovery of new drugs to treat such conditions as Alzheimer’s disease and other neurodegenerative diseases, cancer, diabetes, and a variety of autoimmune and infectious diseases. It uses the latest cutting-edge technologies to speed the drug discovery and development process.

Four Stars, CONTINUED

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 Development 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.”



Rendering of new Scripps Florida Advanced Technology Administration Building



Rendering of the new Scripps Florida campus

Study Offers Innovative Profile of Enzyme That Aids Tumor Growth

> Using an innovative profiling strategy, scientists at The Scripps Research Institute have characterized an enzyme that is “highly elevated” in aggressive human tumor cells.

When the enzyme, KIAA1363, was inactivated, it impaired tumor growth and migration in both ovarian and breast cancer cells, suggesting that inhibitors of this enzyme may prove valuable in the treatment of multiple types of cancer.

The study was the cover story of the October 23 issue of the journal *Chemistry & Biology*.

“Using a combination of enzyme activity and metabolite profiling, we determined that this protein—whose function was previously unknown—serves as a key regulator of a lipid signaling network that contributes to cancer,” said **Benjamin F. Cravatt, Ph.D.**, a Scripps Research professor and a member of its Skaggs Institute for Chemical Biology who led the study. “The heightened expression of KIAA1363 in several cancers indicates that it may be a critical factor in tumorigenesis. In addition, network components, including KIAA1363 itself,

might be considered potential diagnostic markers for ovarian cancer.”

To date, understanding the roles of uncharacterized enzymes in cell physiology and pathology has remained problematic. Typically, the activities of enzymes have been studied *in vitro* using purified protein preparations. The outcome of these test-tube studies can be difficult to translate into clear characterizations of the roles that enzymes play in living systems, where these proteins generally operate within larger metabolic networks.

A primary advantage of metabolite profiling in natural biological systems



“... this protein—whose function was previously unknown—serves as a key regulator of a lipid signaling network that contributes to cancer.”

Dr. Benjamin F. Cravatt

is that it circumvents some of the most time-consuming steps that accompany *in vitro* enzyme analysis while generating data more directly related to their naturally occurring activities.

The team drew both on proteomics—the large-scale study of the structure and function of proteins—and metabolomics—the systematic study of cellular processes, specifically their small-molecule metabolite profiles—to begin to decipher the complex metabolic and signaling networks of cancer.

“The success of our study opens the door to assembling the full range of enzymes into both metabolic and signaling networks contributing to complex pathologies like cancer,” Cravatt said. “This could lead to the discovery of new markers for diagnosis and targets for treatment.”

This work was supported by the National Institutes of Health, the California Breast Cancer Research Foundation, the ARCS Foundation, the Life Sciences Research Foundation, the Burroughs Wellcome Fund, and the Skaggs Institute for Chemical Biology at Scripps Research.

Study Uncovers New Sensor—

A Potential Target for New Therapies for Obesity and Diabetes, and Implications for Heart Disease and Stroke

In a new study, scientists at The Scripps Research Institute and the Genomics Institute of the Novartis Research Foundation (GNF) have described for the first time a glucose activated sensor that acts as a

switch to decrease production of endogenous glucose in the liver, and increase conversion of glucose to fat for storage in adipose tissue. This dual action makes the sensor, Liver X Receptor, a potential target for new

therapies aimed at obesity and diabetes. The research may also have implications for heart disease and stroke.

In the study, glucose is shown to stimulate the activity of the Liver X Receptors (LXR) a and b. The LXRs act as sensors of dietary components, orchestrating the body’s response to nutrients such as oxysterols (short-lived derivatives of cholesterol) and controlling gene expression linked to cholesterol and fat metabolism.

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“When you eat, glucose pours into the gut and is recognized by LXR in the liver, which then activates expression of the enzymes that turn excess glucose into triglycerides that are stored as fat,” said Assistant Professor **Enrique Saez, Ph.D.**, a Scripps Research scientist who led the study, which was supported by GNF.

“The fact that our study demonstrates that LXR does both—it binds to glucose and it induces fatty acid synthesis—is significant and makes LXR a potential target for diabetes and obesity treatments.”

In some recent animal studies, Saez pointed out, activation of LXRs using synthetic molecules also induced regression of atherosclerosis, the clogging, narrowing, and hardening of the body's large arteries and blood vessels that can lead to stroke, heart attack, and eye and kidney problems. Elevated levels of pathogenic cholesterol, also known to bind LXR, are a primary risk for development of atherosclerosis.

“The integration of glucose sensing and control of lipogenesis by LXR may explain why low-fat/high-carbohydrate diets induce hypertriglyceridemia [an elevated level of triglycerides in the blood],” Saez said. “LXR can sense surplus glucose, induce fatty acid synthesis, and prompt the liver's export of triglycerides into the bloodstream. Since LXR acts as the body's sensor of a buildup of pathogenic cholesterol, its ability to bind both glucose and oxysterols suggests that LXR may be a link between hyperglycemia and atherosclerosis.”

In fact, Saez and his colleagues originally looked at LXR as a drug target for atherosclerosis. But when they fed synthetic LXR ligands to mice to induce activation, they discovered that the mice metabolized glucose



“This discovery represents the first signaling pathway where a carbohydrate activates a nuclear receptor, although the precise mode of binding remains unknown.”

Dr. Enrique Saez

more effectively and that activation suppressed new production of glucose in the liver.

That prompted the scientists to look more closely at glucose levels as the LXR activating mechanism in the liver.

To their surprise, what Saez and his colleagues discovered was that glucose bound directly to LXR. This was unexpected because the carbohydrate does not conform to the standard definition of a typical ligand that activates nuclear receptors, transcription factors that coordinate gene expression in response to hormonal and environmental signals. This discovery, Saez said, represents the first signaling pathway where a carbohydrate activates a nuclear receptor, although the precise mode of binding remains unknown.

As part of the study, mice were put on exclusive sucrose or D-glucose diets; all diets were devoid of cholesterol to minimize naturally occurring oxysterols. D-glucose and GW3965 (a synthetic LXR activator) induced similar changes in hepatic gene expression, indicating that LXR functions as a glucose sensor *in vivo* that responds to increasing liver glucose uptake. The ability of the LXRs to respond to glucose and its derivatives was very specific: no effect was seen in other nuclear receptors tested.

The current study focused primarily on the role of glucose sensing in the liver and gut. New studies will focus on the question of whether glucose levels in other tissue types, such as the pancreas, activate LXR, Saez added.

One Person's Legacy Can Make a Difference

You are cordially invited to join the Scripps Legacy Society, whose members are committed to supporting Scripps Research and have included The Scripps Research Institute in their estate plans. The Scripps Legacy Society symbolizes one generation sharing their resources and values with future generations.

We invite Scripps Legacy Society members to join us for the annual Legacy Society lunch in May at the Beckman Center for Chemical

Sciences on campus in La Jolla. The event will feature a discussion of research success stories at the Institute, as well as laboratory tours. Join us!

For more information, please contact Cheryl H. Dean, Esq., our Planned Giving Counsel at (858) 784-2380, or cdean@scripps.edu.



New Index Ranks Scripps Research Faculty Number One in Biophysics; Immunology, Biochemistry in Top Ten

> A new index of graduate program faculty published in *The Chronicle of Higher Education* ranks The Scripps Research Institute's Kellogg School of Science and Technology as best in the nation in biophysics.

Kellogg School faculty also ranked second in Immunology and seventh in Biochemistry.

The new ranking system, called the Faculty Scholarly Productivity Index, rates faculty members' scholarly output

at more than 7,000 doctoral programs across the United States. The index, which was developed jointly by the State University of New York at Stony Brook and for-profit company Academic Analytics, uses data such as

faculty publications, grants, and honors and awards to rank productivity.

Scripps Research launched its graduate program in 1989. Since then, the program has grown rapidly in both size and reputation, now consisting of some 200 students of the biological and chemical sciences. The Kellogg School has also been ranked in the top ten for these disciplines by *U.S. News and World Report*.

Linda Curtiss Wins Distinguished Achievement Award

Linda Curtiss, Ph.D., a professor in the Scripps Research Department of Immunology, has received the American Heart Association's Council on Arteriosclerosis, Thrombosis and Vascular Biology Distinguished Achievement Award.

The association honored Curtiss for "immense contributions to the



Dr. Linda Curtiss

council for many years," according to Alan Daugherty, chair of the council and Gill Foundation Chair of Preventive Cardiology at the University of Kentucky. "Under her leadership, the council has made great strides," he said.

The council presents its Distinguished Achievement Award annually to a member who has made "substantial professional contributions" to arteriosclerosis, thrombosis, or vascular biology and substantial contributions to the council.

Curtiss's research examines the role of innate immunity in atherosclerosis using bone marrow transplantation in atherosclerosis models. Curtiss (Ph.D., University of Washington, Seattle) is currently associate editor of the *Journal of Lipid Research*, an editorial board member of *Arteriosclerosis, Thrombosis, and Vascular Biology*, and an adjunct professor at San Diego State University.



Dr. Ian Wilson

Ian Wilson Appears on PBS

Professor **Ian Wilson, Ph.D.**, was featured in an episode of *NOVA scienceNOW*, on November 21 on PBS. Wilson spoke on his work on the avian flu virus. The full episode via streaming clips is viewable on www.pbs.org/wgbh/nova/sciencenow/.

Richard Lerner to Receive Honorary Degree from Oxford

Scripps Research President **Richard A. Lerner, M.D.**, is one of nine leading figures from the world of science, politics, and the arts set to receive an honorary degree from the University of Oxford this year. Lerner and other honorees from around the world will come to Oxford to receive their degrees at Encaenta, the University's annual honorary degree ceremony, to be held on June 20.

Lerner is receiving the degree of Doctor of Science, *honoris causa*. He is a research chemist, the Lita Annenberg

Hazen Professor of Immunochemistry, Cecil H. and Ida M. Green Chair in Chemistry, and a member of the Skaggs Institute for Chemical Biology at Scripps Research. He is best known for his work in the field of catalytic antibodies which has shown that antibodies can be employed as enzymes — research which has relevance for such conditions as atherosclerosis and Alzheimer's disease. Today, about 55 percent of all new drug applications are antibodies.



Scripps Research President
Dr. Richard Lerner

Cycling for a Cure

> On Monday, January 22, Kyle Bryant was on The Scripps Research Institute's La Jolla campus looking ahead to 2,800 miles of road, stretching from the Pacific Ocean to Memphis, Tennessee.

Bryant, who suffers from the rare genetic disease Friedrich's ataxia — one of the topics of investigation in Scripps Research labs — planned to cover the territory on his modified bicycle, raising awareness and research funds for his disorder along the way.

Bryant averaged 60 miles a day for two months, arriving in Memphis in time for the March 20 meeting of the National Ataxia Foundation.

"Nobody knows about ataxia (even doctors as I found out)," says Bryant, who works as an environmental engineer in Sacramento, California. "That is why I am riding across the country. This disease needs some attention. It is estimated that one in every 50,000 Americans has Friedrich's ataxia, yet nobody even knows about it."

Once a robust athlete, Bryant, now age 25, first started having symptoms

of the progressive disease as a teenager. His first signs included trouble walking, reduced hand coordination,



Kyle Bryant speaks with a supporter before setting out on his ride to raise awareness and research funds for Friedrich's ataxia

and slurred speech. It took over a year of doctor's visits and lab tests to get an accurate diagnosis.

"He gets a lot of stares," said Bryant's father, Mike. "He looks like a drunk, basically. If he goes into a bar, they think he's already drunk."

Barring a medical breakthrough, Bryant will be confined to a wheelchair within a few years.

"It is estimated that one in every 50,000 Americans has Friedrich's ataxia, yet nobody even knows about it."

"I am doing this because I am one of the lucky few Ataxians who can still get around without the use of a wheelchair," Bryant says. "The ability that I have will be gone at some point, so I feel an obligation to do as much as I can while I still can."

Scripps Research Professor **Joel Gottesfeld, Ph.D.**, is leading one
(continues on page 7)

Partners



The Frontiers in Science series continued this fall at the Hilton La Jolla Torrey Pines with a presentation by Scripps Research Professor Katja A. Van Herle, M.D., M.S.P.H., Director of Community Health and Education on “The War Within — Doing Battle with the Obesity and Type 2 Diabetes Epidemics.” Van Herle discussed an innovative new collaboration between Scripps Research and McDonald’s to fight the critical health issues of childhood obesity and Type 2 diabetes through scientific research and educational initiatives. The series features lectures from Scripps Research scientists followed by a reception, where participants can mingle and ask further questions of the researchers. Pictured at the event (left) is donor **Bess Lambron**.

Scripps Florida Associate Director and Head of Lead Identification, **Peter S. Hodder, Ph.D.**, presented to an audience of corporate and private donors at a recent Scripps Florida Corporate Club luncheon. Dr. Hodder directs Scripps Research’s high-throughput screening (HTS) laboratory located in Jupiter, Florida. This process is one of the first and most crucial jobs in the development of novel drug candidates by narrowing the playing field to those few compounds that show promise for drug development. Pictured above are Scripps Research Trustee **Alex Dreyfoos** and his wife, **Renate**; with Dr. Hodder, and Founders’ Circle and corporate club member **Leo Vecellio**, of the Vecellio Group, with his wife **Katie**.

Cycling, CONTINUED

effort to investigate the causes of and possible treatments for Friedreich’s ataxia. He and his colleagues recently provided evidence for one method that might be used to reverse Friedreich’s ataxia. Gottesfeld hopes to have drugs that can treat Friedreich’s ataxia enter into clinical trials on humans within a few years.

“Many people would sit back and take this disease as it comes,” said Gottesfeld. “Kyle’s fighting back with all he has. I really admire his tenacity.”

Another cyclist for the Friedreich’s cause, Frank Wootten of Hooksett, New Hampshire, recently completed a coast-to-coast journey, also to bring attention to the disease. Wootten’s trip

was inspired by his son, TK, who is in a wheelchair and gets around with the help of his service dog, James Bond.

“My helmet’s off to Kyle and his courageous endeavor,” said Wootten.

The Scripps Council of 100

> The Scripps Council of 100 consists of individuals, couples, and representatives of corporations or foundations that contribute \$100,000 annually or make a single contribution of \$1 million or more to The Scripps Research Institute.

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