

Scripps Florida 2012 Scientific Report  
October 1, 2011 – September 30, 2012

## **Part 1: New Faculty and Scientific Administration**

### **Two Noted Scientists Appointed to Scripps Research Metabolism and Aging Department**

The Scripps Research Institute has appointed Paul D. Robbins as a professor and Laura J. Niedernhofer as an associate professor in the Metabolism and Aging Department on the institute's Florida campus.

"It is a distinct honor to welcome these two exceptional scientists to the faculty," said Roy Smith, chair of the Metabolism and Aging Department. "They both bring a wealth of knowledge and experience and are involved in research that will help change the way we deal with aging and disease in the future."

Prior to joining Scripps Florida, Robbins was a professor at the University of Pittsburgh School of Medicine; Niedernhofer was associate professor at the University of Pittsburgh and its cancer institute.

#### *Paul Robbins: Focusing on Age-Related Degenerative Diseases*

In his research program, Robbins focuses on various biological approaches to understanding and treating age-related degenerative diseases, including cancer, bone healing, and diabetes. He has developed a gene therapy approach to arthritis, and is participating in a clinical trial for osteoarthritis—a project he expects to continue at Scripps Florida. His laboratory is also studying a novel peptide for bone treatment.

Mostly recently, he has been using genetic and pharmacologic approaches to inhibit NF- $\kappa$ B, a protein factor that controls DNA transcription. NF- $\kappa$ B is involved in a number of key processes, including immune and inflammatory responses, and has been implicated in diseases ranging from cancer and arthritis to various neurodegenerative diseases.

"It's an honor to join the Scripps Florida faculty," Robbins said. "The quality of the research is spectacular, not to mention the collaborative atmosphere and the outstanding facilities. On top of all that, I grew up in Florida, so this is like a homecoming."

Robbins, 54, received a BA in biology from Haverford College, Pennsylvania, in 1980 and a PhD in molecular biology from the University of California, Berkeley, in 1985. He conducted postdoctoral work at the Whitehead Institute at the Massachusetts Institute of Technology from 1986 to 1990.

Robbins joined the University of Pittsburgh School of Medicine as an assistant professor in the Department of Molecular Genetics and Biochemistry in 1990 and was appointed

associate professor in 1996. He became a professor in the Department of Orthopedic Surgery in 2001.

Robbins' honors and awards include the Synos Foundation Research Award (2000), the Nicolas Andry Award (2004), the Orthopedic Research Society Kappa Delta Award (2005), and the Juvenile Diabetes Research Foundation Mary Jane Kugel Award (2009).

### *Laura Niedernhofer: Exploring the Link between Aging and DNA Damage*

Niedernhofer is interested in the relationship among DNA, cancer and aging—especially the link between aging and DNA damage. She has focused much of her work on a rare and fatal human disorder known XFE progeroid syndrome. Patients rapidly develop progressive symptoms that are associated with old age such as heart disease, muscle wasting and bone loss.

"I'm thrilled to be joining Scripps Florida," Niedernhofer said. "All of us became scientists because we wanted to change healthcare, and we all have ideas about how to do just that—here we have a chance to get them off the shelf and into practice."

Niedernhofer, 47, received a BS in chemistry from Duke University in 1985 and a master's in physiology from Georgetown University in 1991. She was awarded a PhD in biochemistry from Vanderbilt University School of Medicine in 1996 and an MD from Vanderbilt just two years later. She conducted postdoctoral work at Erasmus Medical Center in the Netherlands from 1999 to 2003.

In 1999, she received a National Science Foundation International Research Fellow Award that was followed the next year by an American Cancer Society Postdoctoral Fellowship. In 2005, she became a Hillman Fellow at the University of Pittsburgh Cancer Institute (2005-2008) as well as being named a New Scholar in Aging by The Ellison Medical Foundation (2005-2009).

Both Robbins and Niedernhofer live in Juno Beach.

### **Scripps Research Appoints Cancer Biologist**

The Scripps Research Institute has appointed Christoph Rader as an associate professor in the Department of Cancer Biology and the Department of Molecular Therapeutics.

Before coming to Scripps Florida, Rader was a senior scientist at the National Cancer Institute (NCI) in Bethesda, Maryland. Prior to that, he was an assistant professor on the La Jolla, California, campus of Scripps Research.

"We want to welcome Christoph back to Scripps Research," said John L. Cleveland, chair of the Scripps Research Department of Cancer Biology. "In California, his groundbreaking

antibody research helped pioneer a hybrid cancer therapy, and at NIH he was responsible for developing several innovative approaches to antibody drug and target discovery. He's a great addition to our department and to the institute as a whole."

"It's a great pleasure to return to Scripps Research—and to be part of Scripps Florida," said Rader, 46, who lives with his wife and two sons in Jupiter. "The faculty here is terrific, not only in cancer biology, but also in molecular therapeutics and chemistry. What I missed most at the NCI was being able to work more closely with chemists—they were 45 minutes away. Now, chemists are minutes from my office."

Rader has already taken advantage of that proximity, launching collaborations with Scripps Florida chemists William R. Roush and Thomas Kodadek.

Rader's research is focused on developing antibody therapies to treat cancer. "Monoclonal antibody therapy of cancer is a tremendously exciting and rewarding field that thrives on multidisciplinary expertise in biology, biochemistry, chemistry, pharmacology, and medicine," said Rader. "Prompted by current knowledge, we have gone back to the drawing board to design, engineer, test, and deliver the next generation of monoclonal antibodies that target cancer cells with even higher precision and potency. Scripps Florida is an ideal place for hanging our drawing board and developing novel technologies at the interface of chemistry and biology."

Rader studied biochemistry and molecular biology at the University of Bayreuth in Germany (1986-1988) and at the University of Zurich in Switzerland (1988-1995), where he graduated with a diploma in biochemistry in 1991. In 1995, he was awarded a PhD with honors from the University of Zurich for his work on immunoglobulin superfamily molecules.

Rader did postdoctoral work with Professor Carlos F. Barbas III at Scripps California, where he specialized in antibody engineering, phage display, and catalytic antibody technologies. Following his promotion to assistant professor at Scripps Research in 1999, he won the prestigious Investigator Award from the Cancer Research Institute in 2000. Shortly after, he was part of a Scripps Research team that invented the concept of chemical programming of monoclonal antibodies to generate hybrid cancer therapeutics, a cross between traditional small molecules and a certain type of monoclonal antibody. After commercialization, this innovation has brought several new drugs into phase I and II clinical trials for the treatment of various cancers and metabolic diseases.

Rader joined the NCI in 2003 to head the Antibody Technology Section in the Experimental Transplantation and Immunology Branch. In 2007, he received the NCI Director's Intramural Innovation Award for Principal Investigators for a novel chemical programming concept. His achievements include more than 80 publications and 13 patents or patent applications in the area of antibody engineering and conjugation technologies.

## **Two Distinguished Scientists Appointed to Scripps Research Cancer Biology Faculty**

The Scripps Research Institute has appointed Joseph Kissil as an associate professor and Matthew Pipkin as an assistant professor, both in the Department of Cancer Biology.

“It’s a pleasure to announce the appointment of these two terrific investigators who are pushing the envelope in their respective fields,” said John Cleveland, a Scripps Research professor and head of the Department of Cancer Biology. “Joe works on regulators that cause lung, pancreas, and liver cancer, and a rare tumor called neurofibromatosis, and upon the tumor microenvironment, while most of Matthew’s studies are focused on epigenetic control of cytotoxic T cells and memory T cells, which are essential for immune surveillance in cancer and in combating infectious diseases. The new arenas being tackled by these talented investigators are critical to the future development of new and more effective cancer treatments. We extend a warm welcome to them both.”

### *Joseph Kissil*

Prior to joining Scripps Florida, Kissil, 45, was an associate professor at The Wistar Institute in Philadelphia, PA, as well as a member of the Graduate Group in Cell and Molecular Biology at the University of Pennsylvania.

“At Scripps Florida there are few barriers between scientists—you have chemistry, drug metabolism, and basic biology research, all geared to collaboration,” said Kissil, who lives in Jupiter. “On top of that, the translational research institute and services such as the high throughput screening core make a fantastic combination.”

Kissil received a bachelor’s degree in biology from Ben-Gurion University in Israel and a PhD in molecular biology from the Weizmann Institute of Science, Israel. He did postdoctoral work at the Massachusetts Institute of Technology.

In 2001, he received a Young Investigator Award from the Neurofibromatosis Foundation and in 2003, the R.L. Kirchstein National Research Service Award. In 2010, Kissil was named an American Cancer Society Research Scholar.

Kissil’s work focuses on the mechanisms that maintain normal tissue balance and how these become deregulated in cancer. Kissil has long been interested in the role the tumor microenvironment plays in cancer growth and how the deregulation of various signaling pathways, such as those that relay information from the extracellular environment into the cell interior, can contribute to the disease. “We’re interested in the molecular basis for disease, particularly cancer,” he said. “As we made discoveries, we decided we wanted to take that extra step into translation of the science to potential therapies. To accomplish that, Scripps Florida was the obvious choice.”

### *Matthew Pipkin*

Before joining Scripps Florida, Pipkin, 37, held a junior faculty position at the La Jolla Institute for Allergy and Immunology.

Pipkin, a Florida native who now lives in Juno Beach, received a bachelor's degree in microbiology and immunology from the University of Miami in 1998, and a PhD in microbiology and immunity in 2005 from the same institution. He did postdoctoral training at Harvard Medical School.

"It's an honor to become part of Scripps Florida," Pipkin said. "Coming back to Florida was a big draw, and Scripps Florida is at the leading edge of what science and the state has to offer—plus it has an entrepreneurial spirit that I found nowhere else."

Pipkin's research interests are in the study of chromatin, the cluster of proteins that compact the DNA of chromosomes in the cell nucleus; like a meticulous butler, chromatin dynamically packs the DNA in different ways in different cell types to help prevent damage and to help ensure that only certain genes are accessible for transcription as cells become more specialized. His lab specifically focuses on understanding how chromatin regulates accessibility to genes that promote the differentiation of cytotoxic lymphocytes, immune system cells that directly kill cancer cells.

"My research dovetails with the reasons I came to Scripps Florida and to cancer biology," he said. "We want to understand the basics of how chromatin controls gene expression, and how that underlies cell differentiation—cancer is in many ways an aberrant form of differentiation, which at its roots is a gene expression problem and controlled by chromatin. Second, we want to use what we know about cytotoxic lymphocyte differentiation to develop new therapies and vaccines that elicit durable cytotoxic lymphocyte responses. The resources and faculty here will let us try some bold new approaches."

### **Scripps Research Appoints Noted Autism Researcher to Neuroscience Faculty**

The Scripps Research Institute has appointed Damon Page, PhD, as assistant professor in the Department of Neuroscience.

Page, 36, will work on the Scripps Florida campus in Jupiter. Prior to his appointment, he was a senior analyst at the Allen Institute for Brain Science in Seattle, Washington.

"Damon's research on autism makes a valuable addition to our department," said Ron L. Davis, chair of the Department of Neuroscience. "His discovery of genes that can cause autism-like symptoms is a breakthrough in the complex origins of the disease and offers new potential therapeutic targets to investigate. We're delighted he is joining us."

"This is a wonderful opportunity to be part of a dynamic, highly collaborative organization, with a breadth of basic and translational research that meshes perfectly with my research,"

Page said. "Scripps Florida is a unique place to explore the basic science of how the brain develops and then to use that knowledge to develop potential new treatments for autism."

Page, who lives in Jupiter, received his bachelor's degree in biology from Eastern Oregon University in 1999 and his PhD from the University of Cambridge in 2002. He was a postdoctoral fellow at the MRC Laboratory of Molecular Biology from 2002 to 2004 and the Massachusetts Institute of Technology (MIT) from 2004 to 2009; he worked as a research scientist at MIT from 2009 to 2010.

It was during his stint at MIT that Page led a groundbreaking study that resulted in the discovery of a novel mechanism whereby two autism risk factors interact to shape autism-like symptoms in an animal model. That discovery showed for the first time that genes acting in two distinct molecular pathways implicated in autism can interact to significantly influence the severity of symptoms. The study pointed to the intersection of these pathways as a potential new target for therapeutic development.

Autism is a complex neurodevelopmental disorder that impairs the normal development of social and communication skills, among other facilities. Autism is the most severe form of autism spectrum disorders; milder forms include Asperger syndrome. According to the National Institutes of Health, six children out of every 1,000 have autism spectrum disorder, with males four times more likely to be afflicted than females.

"There are a number of risk factors for autism," Page said, "but at present we don't understand how these interact in the developing brain to cause the disorder. My aim is to shed light on this problem, but, more importantly, to apply what we learn in the laboratory to help individuals and families affected by the disorder."

For more information, see Page's faculty web page at <http://www.scripps.edu/research/faculty/page>

## **Dynamic Neuroscientist Joins Scripps Research**

The Scripps Research Institute has appointed Srinu Subramaniam, PhD, as an assistant professor in the Department of Neuroscience. Subramaniam, who investigates the signaling networks involved in neurodegenerative diseases, was a research associate in neuroscience at Johns Hopkins University prior to joining Scripps Research.

"It's a great honor to join the Scripps Florida faculty," he said. "When I first visited, I was impressed with the science and the people—they were all highly focused, highly energized. Many are working on the same types of problems I am but taking different paths, so the possibility of collaboration is exceptional."

“Srini is a dynamic researcher who will continue to make remarkable inroads in the science of neurodegenerative diseases,” said Ron Davis, chair of the Department of Neuroscience. “We want to extend a warm welcome to him and his family.”

Subramaniam received a bachelor’s degree in chemistry, botany, and zoology in 1992 from the University of Bangalore, India, and a PhD in neuroscience in 2004 from the University of Heidelberg, Germany, graduating summa cum laude. He also received the German Anatomical Society’s Wolfgang-Bargmann Prize, and the Young Investigator Award from the University of Heidelberg.

During his graduate studies, Subramaniam founded the Samatva Trust for Rural Education in Bangalore. The trust’s goal is to support children who excel in school but cannot pursue further education due to lack of financial support. More than a thousand students have benefited from the scholarship program. For more information, please visit [www.samatvatrust.org](http://www.samatvatrust.org)

Subramaniam completed his postdoctoral work at Johns Hopkins University. In 2010, the Johns Hopkins School of Medicine honored him with the Daniel Nathan Research Award. At Scripps Florida, Subramaniam’s laboratory will focus on finding target genes involved in neurodegenerative diseases such as Huntington’s, Parkinson’s, and Alzheimer’s and developing novel therapeutics to treat them.

Subramaniam, who led the Johns Hopkins research team, uncovered the cause of brain specific damage that occurs in Huntington’s disease, a hereditary neurodegenerative disorder that affects some 30,000 Americans. In Huntington’s disease the selective brain region called striatum is damaged and the cause for this selectivity was unknown. In 2009 article in the journal *Science*, Subramaniam and his colleagues pinpointed a protein known as Rhes that is prevalent in the striatum as responsible for striatal damage in Huntington’s disease; Huntington’s patients often suffer from uncontrollable movement and cognitive deficits due to degeneration of striatum. Subramaniam’s findings not only explained the cause for striatal damage in Huntington’s disease, but also its unique mechanism of action, and suggested a potential new therapeutic target.

In a 2011 *Nature Neuroscience* study, Subramaniam found that Rhes is also involved in the uncontrollable movement, a side effect that occurs during the treatment for Parkinson’s disease. Subramaniam’s studies suggest that drugs targeted at Rhes could mitigate multiple symptoms and may have therapeutic value in more than one brain disease.

Ultimately, Subramaniam is working towards a better understanding of how various neurodegenerative diseases, including Alzheimer’s disease and spinal muscular atrophy, as well as Huntington’s and Parkinson’s, develop different pathologies as they progress. “We want to understand the signaling networks that mediate the selective vulnerability of brain cells to design better therapeutic strategies to prevent or slowdown these debilitating neurodegenerative disorders,” he said.

Subramaniam lives with his wife, Neelam Shahani, PhD, who is also a neuroscientist, and two daughters, six-year-old Vyapti and 14-month-old Anvika, in Jupiter, Florida.

### **Scripps Florida Appoints Innovative Neuroscientist**

The Scripps Research Institute has appointed Brock Grill as an assistant professor in the Department of Neuroscience. Previously, Grill was a member of the Department of Pharmacology at the University of Minnesota.

“We’re extremely pleased to have Brock join our department,” said Ron Davis, chair of the Scripps Research Department of Neuroscience. “His innovative work on neuronal and synapse development will help us get to the bottom of how the brain develops, and what exactly goes wrong in conditions of abnormal brain development.”

“I’m excited about joining Scripps Florida,” said Grill, who lives in West Palm Beach, FL. “The resources here, particularly the drug screening technology, are exceptional and will help tremendously in expanding my research. In addition, Ron Davis is doing a superb job of assembling a great neuroscience faculty—I was onboard very early on after hearing Ron’s vision for the department and meeting the talented people he had hired.”

Grill received a bachelor’s degree in Microbiology from the University of Alberta, Canada, in 1998, and a PhD in Experimental Medicine from the University of British Columbia in 2003. He conducted postdoctoral work at the University of California, Santa Cruz from 2004 to 2007 and Stanford University from 2007 to 2009.

Grill’s research is focused on understanding how different events in neuronal development are coordinated on a molecular level. The formation and wiring of the brain requires the intricate interplay of a series of complex molecular events. By unraveling the molecular mechanisms that govern neuronal development in the roundworm *C. elegans*, Grill said he hopes to gain insight into how neurons manage numerous signals from their environment to form a neural network. Such knowledge has tremendous potential to help generate new therapies to treat neurodegenerative diseases, as well as injury to the central nervous system from stroke and trauma.

### **NIH Executive Selected to Head Scientific Operations for Scripps Florida**

The Scripps Research Institute has named Dawn Johnson, PhD, currently with the National Institutes of Health (NIH), as senior director of scientific operations for the Scripps Florida campus.

“As the campus continues to expand as a center of scientific excellence, Dawn brings her experience as a scientist, knowledge of the federal funding process for research, and talents



as a manager to Scripps Florida,” said Scripps Research President Michael A. Marletta. “We want to offer her our warmest welcome.”

“I’m delighted to be joining Scripps Florida,” said Johnson, “and look forward to working at such a dynamic scientific institution.”

Johnson, age 40, is currently the associate director for science management in the Office of the Scientific Director at the National Institutes of Mental Health (NIMH) Intramural Research Program. The program, with an annual budget of \$168 million, includes 47 active clinical and basic labs and eight core facilities. Since joining the NIH in 2002, Johnson has won several NIMH and NIH Director awards for her work on planning and communications projects.

A native of Atlanta, Johnson earned an associate’s degree in liberal arts from the Oxford College of Emory University in 1991, a BS from Georgia State University in biology in 1993, and a PhD in neuroscience from the University of Wisconsin, Madison, in 1999. She also received a certificate in public health policy from George Washington University in 2005. Johnson is excited to return to Florida, having participated in postdoctoral training in two labs at the University of Miami from 1999 to 2002. She also has family in Palm Beach County.

Johnson starts her new position at Scripps Florida on May 7, 2012.

Johnson replaces Harry Orf, who headed the Jupiter campus from its inception until last month when he returned to Massachusetts General Hospital in Boston to manage scientific research operations there.

## **Part 2: Grant Awards and Licensing Agreements**

### **Scripps Florida Scientists Awarded \$8.4 Million Grant to Develop New Anti-Smoking Treatments**

Scientists from the Florida campus of The Scripps Research Institute has been awarded an \$8.4 million grant from the National Institute on Drug Abuse of the National Institutes of Health (NIH) to develop new compounds to help prevent relapse in smokers who are kicking the habit.

The new five-year NIH award is a program project grant, which is designed to support an institutionally based research program with a well-defined research focus that requires several interrelated subprojects as part of the overall study.

Paul Kenny, a Scripps Research associate professor, is the program director and principal investigator for the study.

“This really is a broad-based, multi-disciplinary team effort,” Kenny said. “We’ve assembled a team of first-class scientists at Scripps Florida with all the experience necessary to develop novel therapeutics for the treatment of tobacco abuse.”

Others involved in the study are Michael Cameron, Theodore Kamenecka, and Patricia McDonald of The Translational Research Institute on the Scripps Florida campus.

Tobacco smoking is a global scourge, killing more than 5 million people each year worldwide, according to the World Health Organization. It is estimated that if current trends continue, by 2020 smoking will become the largest single health problem worldwide. The World Bank estimates that in high-income countries, smoking-related healthcare accounts for between 6 and 15 percent of all healthcare costs, some \$160 billion annually.

Nicotine addiction is notoriously hard to break. Even with the most effective smoking-cessation agents available, more than 80 percent of smokers who quit or attempt to quit will relapse.

To combat these dismal statistics, the study is focused on an entirely new mechanism to help smokers break the habit.

That mechanism is a receptor for a specific neuropeptide (short chain of amino acids found in nerve tissue) that, when blocked, significantly decreases the desire for nicotine in animal models.

The neuropeptide, known as hypocretin-1 or orexin A, initiates a key signaling cascade that maintains tobacco addiction in human smokers. In a 2008 study in the *Proceedings of the National Academy of Sciences*, Kenny and colleagues showed that blocking hypocretin-1 receptors not only decreased nicotine use in animal models, but also abolished the stimulatory effects of nicotine on brain reward circuitries. These results demonstrated that hypocretin-1 plays a major role in driving the desire for more nicotine.

These findings also highlighted the importance of hypocretin-1 receptors in a region of the brain called the insula, a walnut size part of the frontal lobe. While all mammals have insula regions that sense the body's internal physiological state and direct responses to maintain homeostasis, this region has also been implicated in cravings. In one study, it was reported that smokers who sustained damage to the insula lost the desire to smoke, an insight that revealed the insula as key for sustaining the tobacco habit in smokers.

## **Scripps Florida Scientist Awarded \$4.2 Million for Type 1 Diabetes Research**

*Grant Will Fund Research into Early Diagnoses and New Treatment Options*

A scientist at The Scripps Research Institute has been awarded \$4.2 million from the National Institutes of Health in a program to advance what the agency calls “bold and creative research” into Type I diabetes.

Thomas Kodadek, a professor in the Department of Chemistry on the Scripps Florida campus, is the principal investigator on the study. The award will be shared with researchers at the University of Miami and Opko, a Florida-based biotechnology company.

The new four-year grant from the NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is a special Type I Diabetes Impact Award (DP3). Type I diabetes is an autoimmune disease, in which the immune system attacks the body’s own tissues. In Type 1 diabetes, the immune system attacks cells in the pancreas that produce insulin, which leads to insulin deficiency; the condition is treated with regular insulin injections.

The new grant to Kodadek and his colleagues will fund research to determine early autoimmune reactions that drive the development of Type I diabetes, as well as to look for ways to selectively block such autoimmune diseases without shutting down or damaging the entire immune response.

“Once the earliest autoimmune reactions have been identified,” Kodadek said, “we can develop compounds that specifically target the autoimmune cells to see if we can block the disease in mice without affecting the normal function of the ‘good’ parts of the immune system. This would set the stage for similar studies in human diabetic patients. Obviously, if we succeed in developing a therapy for humans, it would have a radical impact on the detection and treatment of diabetes—and other autoimmune conditions as well.”

The research funded by the new grant may also lead to new ways to detect Type 1 diabetes. Currently, immunoassays, a technique that detects auto-antibodies for human insulin, are used as early diagnostic markers for Type I diabetes, and for screening and risk assessment in clinical trials. Because progression of diabetes is often haphazard, additional markers are needed to improve overall risk assessment.

The novel approach Kodadek uses in his research involves peptoids, synthetic molecules similar to peptides that make up proteins when joined together. His lab uses these peptoids to screen or search for molecules that bind to and affect the action of a type of immune system molecule called an antibody.

Like the handmade flies used by fishermen, the synthetic peptoids are a lure to capture disease-specific antibodies—in this case, for diabetes—well enough to pull them from blood samples. It’s a novel way to short-circuit the discovery process that has been used successfully in the lab for Alzheimer’s disease. In the new project, once novel autoimmune cells for diabetes have been identified, Kodadek said, the scientists will begin to determine whether they can be turned off selectively, proof-of-principle for what could be a powerful therapeutic strategy.

## **Scientists Share \$3.85 Million NIH Grant to Develop New Class of Cancer Therapies**

*Study Will Focus on Inhibiting a Hallmark of Cancer Cell Metabolism*

A pair of Scripps Research Institute scientists, one a cancer biologist and the other a chemist, has been awarded \$3.85 million from the National Institutes of Health (NIH) to develop a new generation of broad spectrum anti-cancer therapeutics, including breast cancer and lymphoma.

John Cleveland, chair of Scripps Florida's Department of Cancer Biology, and William Roush, chemistry professor, executive director of Medicinal Chemistry, and associate dean of graduate studies at Scripps Florida, are co-principal investigators for the new five-year project.

The focus of the research is on two proteins considered high priority targets for cancer therapeutics, Mct1 and Mct4. These "transmembrane transporters," which specifically transport lactic acid, a byproduct of cancer cell metabolism, out of cancer cells, are expressed at low levels in normal tissues but at high levels in most malignancies.

"This project represents the culmination of three years of collaboration between our two laboratories to design, develop, and validate novel anti-cancer therapeutics targeting these transporters," Cleveland said. "They are a new and unexploited avenue for cancer therapy, a potential Achilles' heel to attack a broad spectrum of tumor types. A lot of malignancies express Mct1 and we think we can tailor these inhibitors to treat afflicted patients."

Mct1 and Mct4 come into play during a process called "aerobic glycolysis," a pathway used by cancer cells to generate energy from glucose and to produce essential building blocks. In cancer cells, this process produces an excess of lactate or lactic acid, which is a predictor of malignancy and even metastasis—the spread of cancer. Cleveland and Roush have shown that targeting Mct1 and Mct4 not only disrupts lactate homeostasis in certain types of lymphoma, but also disables tumor cell metabolism and proliferation.

So far, Cleveland and Roush have developed more than 190 small molecules to inhibit Mct1. With the new grant, the scientists plan to optimize these Mct1 inhibitors, synthesize new small molecule inhibitors of Mct4, and to devise new approaches to selectively deliver these agents to cancer cells.

"This is an example of the very best kind of collaboration at Scripps Research," Roush said, "leading from discoveries in cancer biology to the development of novel compounds through the work of the Medicinal Chemistry and the Pharmacokinetics groups to produce an entirely new generation of cancer therapeutics."

In the new project, the scientists will also explore the roles played by Mct1 and Mct4 in lymphomas and breast cancer driven by the Myc oncoprotein, which is activated in approximately 70 percent of all human cancers.

## **Scripps Florida Scientist Awarded \$3.4 Million for HIV/AIDS Research**

*Grant Will Fund Study of New Drug Target and Treatment Options*

A scientist at The Scripps Research Institute has been awarded \$3.4 million from the National Institutes of Health to study the mode of action and the therapeutic potential of a new compound that blocks a step of HIV replication not targeted by current therapies.

Susana Valente, an assistant professor at Scripps Florida, is the principal investigator of the five-year grant. Valente will lead research into the viral protein known as Tat, a potent activator of HIV gene expression, and a Tat inhibitor that is extremely effective at reducing viral output from acutely and chronically infected cells in culture. Most antiretroviral compounds only block new infections; a Tat inhibitor can reduce viral replication from cells already infected.

“Our main goal with this grant is to fully understand the underlying mechanism of this new compound’s inhibitory strength against Tat,” Valente said, “and then to evaluate its therapeutic potential in animal models. If that’s successful, the next obvious step would be to optimize it for use in human clinical trials.”

Despite recent advances, HIV/AIDS continues its deadly global march, affecting more than 35 million individuals worldwide. The virus stubbornly persists in infected subjects despite Highly Active Antiretroviral Therapy (HAART). This residual viremia is the major hurdle for HIV eradication. Valente’s newly identified Tat inhibitor defines a novel class of anti-viral drugs that could potentially inhibit viral production from stable reservoirs and reduce viral persistency during HAART.

“Initially, we thought this compound was targeting another protein, but the data suggested that it was actually an inhibitor of Tat,” Valente said. “We soon discovered we had a powerful inhibitor of HIV-1 transcription in our hands—and that’s where we are today. This work was made possible by the great ongoing collaboration with Professor Phil Baran of Scripps California.”

## **Scientists Awarded \$3 Million to Develop New, More Effective Pain Treatments**

Scripps Florida scientists have been awarded \$3.1 million by the National Institute on Drug Abuse, part of the National Institutes of Health, to study and develop several new compounds that could prove to be effective in controlling pain without the unwanted side effects common with opiate drugs, such as morphine, *Oxycontin*®, and *Vicoden*®.

Laura Bohn, an associate professor in the Department of Molecular Therapeutics and Neuroscience at Scripps Research, and Thomas Bannister, an assistant professor in the Department of Chemistry and associate scientific director in the Translational Research Institute at Scripps Research, will serve as joint principal investigators for the new five-year study.

Their study will focus on four new classes of compounds that appear to differ fundamentally from opiates in the side effects that they can produce.

"Once we more fully understand how these compounds work, we expect to optimize and develop them as novel drugs," said Bohn. "We hope to produce potent pain relievers without the problems associated with current treatments."

The adverse side effects of morphine and other opiate drugs can range from the uncomfortable (constipation) to the dangerous (addiction, respiratory suppression, and death by overdose).

While the new compounds bind and activate the same receptor as morphine—the mu opioid receptor or MOR—they do so in a way that avoids recruiting the protein beta arrestin 2. Genetic studies have shown that animal models lacking beta-arrestins experience robust pain relief with diminished side effects.

In an encouraging sign for further development, compounds in the four chemical classes have already been synthesized by Bannister's medicinal chemistry group.

"We designed compounds intended to have biological activity in the brain," said Bannister. "While we expected to find pain relievers, we were thrilled to see that some compounds also had the chemical and biological properties necessary for showing reduced side effects. The added financial support should help us build upon these exciting results and identify safer pain medications."

### **Scientist Receives \$2.8 Million to Study Critical Cell Signaling Mechanism and Develop Potential Therapeutics**

A scientist from the Florida campus of The Scripps Research Institute has been awarded a pair of grants totaling \$2.8 million from the National Institute of General Medical Sciences of the National Institutes of Health, and from TargAnox, a Massachusetts-based biotechnology firm.

Kate Carroll, a Scripps Research associate professor, will be the principal investigator for the new projects.

Research funded by both grants will focus on a process known as sulfenylation, a relatively new field of research. During periods of cellular stress, caused by factors such as UV radiation or chronic diseases such as cancer, the level of highly reactive oxygen-containing

molecules can increase, resulting in inappropriate modification of proteins and cell damage through this process. One oxidant produced naturally in the body, hydrogen peroxide, acts as a messenger that can activate cell proliferation.

In the new research, Carroll will look at cell signaling in sulfenylation and explore ways that it might be modified with potential drug compounds to treat conditions such as lung and breast cancers, as well as be used to diagnose and monitor such diseases.

To explore the process, Carroll and her colleagues have developed a highly selective chemical probe—known as DYn-2— that can detect minute differences in sulfenylation rates within the cell. The new four-year, approximately \$1.5 million NIH grant (award number 1R01GM102187-01) will fund work utilizing that chemical probe to fully define the molecular mechanism through which a key signaling protein, epidermal growth factor receptor (EGFR), is modified by hydrogen peroxide.

“The grant from NIH will let us take a closer look at the basic mechanics of the sulfenylation process and detail how oxidation regulates EGFR,” Carroll said. “The TargAnox study uses that work as a spring board into potential treatments.”

Carroll said she also plans to investigate additional targets of sulfenylation and to test various compounds that can reverse the process.

## **Scientist Awarded \$2.2 Million Grant to Study Hepatitis C**

### *Funding Could Help Identify Underlying Mechanisms of Virally Induced Liver Cancer*

The Scripps Research Institute has been awarded a \$2.2 million grant by the National Institutes of Health (NIH) to determine how the hepatitis C virus (HCV) induces liver cancer. The research could lead to potentially new therapeutic targets for treating those chronically infected with the virus.

Timothy Tellinghuisen, an assistant professor on the Florida campus of Scripps Research, is the principal investigator for the project.

Hepatitis C virus infection is a major public health problem worldwide. Estimates place the number of HCV infected individuals at approximately 170 to 200 million, representing nearly three percent of the world’s population, according to the World Health Organization. HCV infection and its assorted pathologies are responsible for an estimated 250,000 deaths a year worldwide.

A majority of patients remain chronically infected, which can lead to progressive liver damage, cirrhosis, and often the development of hepatocellular carcinoma—liver cancer. An estimated 60 to 70 percent of all those infected develop chronic infections and most

progress to major liver damage. Each year, as many as five percent of these chronically infected patients will develop liver cancer.

While the mechanisms by which HCV induces liver cancer are largely unknown, Tellinghuisen's ongoing research points to host cell signaling pathways that are likely altered by the virus, creating a replication niche for the virus that avoids the body's innate immune system.

"We have identified a host protein—called CARD14—as an important factor for HCV RNA replication," he said. "We believe that a pathway regulated by this protein gets manipulated by the virus to maintain chronic infections and that this contributes, in part, to liver cancer development. The new grant will help us explore the extensive role of CARD14 in HCV replication and, quite possibly, identify new ways to attack chronic HCV infection."

Overall, the new grant will enable Tellinghuisen and his colleagues to characterize how the virus manipulates this host cell pathway, identify the genes regulated by this pathway and determine their effect on viral infection and persistence, and define the function of this protein in normal liver physiology.

## **Scientists Win \$2 Million to Study New Pathway Important in the Development and Maintenance of Lymphoma**

*The Researchers Hope the Project Will Reveal Suitable Drug Targets*

The National Institutes of Health has awarded The Scripps Research Institute \$2 million to study the role of a pathway in the development and maintenance of B-cell lymphoma, a type of cancer that begins in immune system and turns normal disease fighting cells into cancers. The disease affects immune cells known as lymphocytes, which are part of our white blood cells.

John Cleveland, PhD, chair of the Department of Cancer Biology on the Scripps Florida campus, will be the principal investigator for the new five-year study.

B-cell lymphomas tend to occur in older patients and in those people whose immune system has been compromised. It is one of the most common blood cancers in the United States and kills about 20,000 Americans each year.

The new project will focus on the role of Myc oncoproteins—the products of Myc oncogenes—which are activated in over half of all human tumor types. Myc oncoproteins accelerate the rate of cell growth, which increases the risk of acquiring additional mutations that allow a premalignant cell to develop into a full-blown tumor. In this project, the Cleveland lab will investigate the role of a pathway that controls the destruction of a



class of messenger RNAs (mRNAs) that encode proteins that regulate the development and maintenance of tumors.

“This grant allows us to focus on a new pathway that is controlled by Myc that we think is suitable to target for the development of new anti-cancer drugs,” said Cleveland, who has led numerous studies shedding light on this oncogene. “We are very hopeful that learning more about this process will open the door for the development of new treatments.”

Specifically, the new project aims to define the mechanisms by which Myc controls the expression and function of Tristetraprolin or TTP, a mRNA-binding protein that normally controls the destruction of a subset of important mRNAs. Importantly, Research Associate Robert Rounbehler, PhD, and other colleagues in the Cleveland lab have shown that TTP functions as a tumor suppressor that impairs the development and maintenance of B lymphoma. Their findings indicating that agents that regulate TTP or affect its key mRNA targets hold great promise as anti-cancer agents.

### **Esther B. O’Keeffe Foundation Gives \$2 Million to The Scripps Research Institute**

The Esther B. O’Keeffe Charitable Foundation has made a \$2 million donation to The Scripps Research Institute to fund biomedical research and education on the Florida campus. In recognition of the gift, the Founders Room and the adjoining board room at Scripps Florida have been named the Esther B. O’Keeffe Founders Suite.

“I know I speak for the entire Scripps community when I wholeheartedly thank the Esther B. O’Keeffe Charitable Foundation,” said Scripps Research President and CEO Michael A. Marletta. “Gifts of this magnitude are transformative and will go directly towards the next generation of discoveries to understand, cure, and treat human disease.”

“We are delighted to contribute to The Scripps Research Institute’s important scientific and educational work,” said Clare O’Keeffe, executive trustee of the foundation. “These efforts are tremendously exciting and we are proud to be part of them.”

The Esther B. O’Keeffe Charitable Foundation was established in 1990 by the late philanthropist Esther B. O’Keeffe, wife of respected surgeon and philanthropist Dr. Arthur O’Keeffe. Their children now carry on the family tradition by serving as trustees of the foundation, which supports a variety of health and medical research causes, as well as a broad spectrum of arts and cultural programs.

Over the years, the foundation has supported innovative non-embryonic stem cell research at Scripps Research, helping to advance breakthroughs in the development of new treatments for conditions such as diabetes, Alzheimer’s, Parkinson’s, hearing loss, and spinal cord damage.

The new unrestricted gift will be used to fund special initiatives on the Florida campus. In the past, unrestricted funds have provided state-of-the-art scientific infrastructure, funded “out of the box” research projects, provided crucial “bridge funding” for scientists between grants, and enabled graduate students to study in the institute’s top-ranked PhD program.

With this gift, the foundation and its trustees become Scripps Florida Founders, a designation that honors donors who have made lifetime contributions of \$2 million or more to the Jupiter campus.

The O’Keeffe family’s generosity is reflected in the names of many Palm Beach area facilities and programs, including the Esther B. O’Keeffe Art Gallery and Speakers Series at The Society of the Four Arts, pavilions at the Good Samaritan and St. Mary’s medical centers, a wing at the Norton Museum of Art, and the American Heart Association’s West Palm Beach headquarters. In addition, the Esther B. O’Keeffe Charitable Foundation has supported the Georgia O’Keeffe Museum, Massachusetts General Hospital, Cape Cod Hospital, and many other charities.

### **Scientist Awarded \$1.9 Million to Study Food Intake and Metabolism**

A scientist from the Florida campus of The Scripps Research Institute has been awarded \$1.9 million from the National Institutes of Health to study pathways that regulate how we coordinate the timing of our desire for food throughout the day. These pathways play a key role in maintaining the body’s balance between how much we eat and our metabolism and energy expenditure.

Andrew Butler, an associate professor at Scripps Research, is the principal investigator for the new four-year study.

The research focuses on the melanocortin-3 receptor (MC3R, a g-protein coupled receptor) in the central nervous system. The MC3R is one component of the central nervous melanocortin system, which normally responds to signals of nutrient intake. The actions of the central nervous melanocortin system involving MC3Rs are central to the regulation of our metabolism. Attenuated activity of this system has been implicated in a range of metabolic diseases, including obesity and insulin resistance (a precursor to diabetes).

“One function of the melanocortin system is to prevent obesity in humans,” he said, “and this system is therefore considered an attractive target for developing drugs against obesity and eating disorders. Unfortunately, very little is known about the functions of melanocortin-3 receptors.”

Butler’s ongoing research suggests that MC3Rs help synchronize our circadian rhythms (24-hour day-night cycles) with food intake. MC3Rs are also linked to the regulation of glucose production and insulin action during cycles of fasting and feeding.

“Our goal for this new study is two-fold,” Butler said. “We want to identify the MC3R signaling pathways involved in regulating behaviors that anticipate feeding, and we want to look at pathways responsible for maintaining metabolic homeostasis.”

Beyond forming a better understanding of the functions of MC3R in the central nervous system, Butler said, the ultimate point of the research is to develop new and innovative approaches to prevent and treat metabolic and circadian-rhythm disorders.

### **Team Awarded Nearly \$1.5 Million to Develop New Approaches to Treat Cancer**

Scientists from the Florida campus of The Scripps Research Institute have been awarded approximately \$1.5 million from the National Institutes of Health to identify and develop new therapeutic approaches against a broad spectrum of cancers.

John Cleveland, professor and chair of the Department of Cancer Biology, and Derek Duckett, associate scientific director of the Translational Research Institute at Scripps Florida, will act as co-principal investigators.

The new three-year grant will allow the Scripps Florida scientists to develop high-throughput screening tests to identify and optimize inhibitors of the “autophagy pathway,” the principal recycling center of the cell, which is especially active during times of stress or nutrient loss. During autophagy, various cell components, including damaged proteins and mitochondria, are delivered to the lysosome, which is essentially a bag of enzymes that breaks down cellular waste.

Autophagy is critical to cell survival and defects in the pathway can lead to a number of disorders, including some neurodegenerative and muscular diseases.

“We have shown that impairing autophagy can improve the efficacy of anti-cancer drugs, helping to overcome drug resistance,” Cleveland said. “Although there’s a lot of interest in generating compounds to act on specific components of the pathway, none exist now. The new grant will, hopefully, help us begin to remedy that situation.”

Duckett added, “Our studies have shown that impairing the autophagy pathway increases the sensitivity of cancer cells to conventional therapeutics, so this is a highly practical and productive approach to developing potential treatments.”

With the new funding, the scientists will develop a novel biochemical test to identify inhibitors of the UNC-51-like kinase (Ulk1), a critical on-off switch that regulates the pathway. Once identified, these small molecules will also help scientists improve their basic understanding of autophagy, its relationship to cancer, and its use as a target that could enhance the action of conventional anti-cancer therapeutics.

The funding was granted by the National Cancer Institute of the National Institutes of Health under award number CA169142.

## **Scripps Florida Team Awarded Nearly \$1.5 Million to Develop Potent New HIV Inhibitors**

A Scripps Florida team has been awarded nearly \$1.5 million by the National Institutes of Health to identify and develop novel potent inhibitors of the human immunodeficiency virus (HIV), the cause of AIDS.

A. Donny Strosberg, a professor on the Florida campus of The Scripps Research Institute, is the principal investigator for the new three-year study.

Current treatments of HIV-infected patients are based on combinations of drugs—called cocktails—that target several critical key steps in the early and late stages of the viral replication cycle. While these combinations have proven effective in controlling the infection in many patients, the continuous emergence of new multi-resistant viral strains requires the development of new classes of drugs that can be aimed at different targets on HIV.

Strosberg's target is the capsid protein or CA, the primary component of the HIV virion—the infectious particle responsible for transporting the viral genome to host cells. This viral protein forms a cone-shaped shell around the HIV genome, and plays a critical role in the lifecycle of the virus by packaging and organizing the viral genome so that HIV can replicate efficiently.

“Because of the growing resistance of HIV against current treatments, a new, differently targeted approach to treating the disease is urgently needed,” Strosberg said. “We expect to use the HIV capsid protein as a new high-throughput screening target for the discovery of novel anti-HIV/AIDS agents.”

Identifying new compounds that could target the CA protein might make it possible to prevent the protein's assembly into capsid shells in the first place, blocking the virus's infectivity, and adding a potent complement to existing treatments, he said. This strategy has worked well for Strosberg's group, which has in the past years discovered several potent inhibitors of the hepatitis C virus.

Strosberg and his colleagues, who include Susana Valente, PhD, an assistant professor at Scripps Florida, and Massimo Caputi, PhD, an associate professor of biomedical science at the Florida Atlantic University Charles E. Schmidt College of Medicine, plan to perform an initial screening of some 350,000 compounds in the Molecular Libraries Probe Centers Network at Scripps Research; Scripps Research is one of only four such large probe centers nationwide.

## **Two Scripps Research Scientists Win Prestigious NIH Innovator Awards**

*Michael Petrascheck and Brian Paegel Each Will Receive \$1.5 Million*

Two Scripps Research Institute scientists have won prestigious National Institutes of Health (NIH) Director's New Innovator Awards. The recipients are Assistant Professor Michael Petrascheck of the institute's La Jolla, California campus, and Assistant Professor Brian Paegel of the Jupiter, Florida campus.

The awards, which were announced by NIH Director Francis S. Collins at the Seventh Annual NIH Director's Pioneer Award Symposium September 20, will provide each recipient with \$1.5 million in research funding over five years.

"The NIH Director's Award programs reinvigorate the biomedical work force by providing unique opportunities to conduct research that is neither incremental nor conventional," said James M. Anderson, director of the Division of Program Coordination, Planning and Strategic Initiatives, who guides the NIH Common Fund's High-Risk Research program. "The awards are intended to catalyze giant leaps forward for any area of biomedical research, allowing investigators to go in entirely new directions."

Petrascheck, who is a member of the Department of Chemical Physiology, the Department of Molecular and Experimental Medicine, and the Dorris Neuroscience Center at Scripps Research, will use the award to conduct research on aging and lifespan in *C. elegans*, a flatworm widely used in aging research. The project will test strategies that might be used in human therapies.

"The innovator award will allow me to focus more of my attention on science," said Petrascheck. "We now have the means necessary to develop the tools that will allow us to determine how sensory perception influences aging and how sensory perception could be targeted by small molecules to treat age-related disease."

Paegel, an assistant professor in the Department of Chemistry, will use his award to evolve new molecular tools for protein sequencing.

"Imagine being asked to take apart a sophisticated race car with a single Phillips-head screwdriver," said Paegel. "This is basically where we are today with protein sequencing technology. We will evolve a suite of custom-tailored molecular tools that will allow us to identify all sites of protein modification, and to correlate those changes with normal cellular function and disease. Our approach integrates the institute's strengths in chemistry and high-throughput screening with my laboratory's expertise in microfluidic technology development and evolution."

Winners of the NIH Director's New Innovator Award are selected on the basis of individual creativity, the innovativeness of his or her research approaches, and the potential of the proposed project, if successful, to have a significant impact on an important biomedical or

behavioral research problem. More information on the New Innovator Award is at <http://commonfund.nih.gov/newinnovator>, including information on this year's awardees.

### **Scripps Research Scientist Receives \$1 Million Research Grant from Novo Nordisk**

Andrew Butler, an associate professor in The Scripps Research Institute's Department of Metabolism and Aging, has been awarded \$1 million in funding over the next two years to further his research into a novel protein with the potential to improve the understanding and future treatment of diabetes.

The award is notable in that it comes not from the US National Institutes of Health but from Novo Nordisk, an international healthcare company based in Denmark recognized as a world-leader in diabetes treatment. The Novo Nordisk Diabetes Innovation Award Program was launched in 2011 to help scientists substantiate early research efforts that could result in new treatment options for diabetes and obesity.

Butler's two-year research project, entitled the "Investigation of a Novel Peptide Hormone in Diabetes Treatment," was selected from more than 80 submitted proposals from US and Canadian research institutions.

The research involves a peptide hormone secreted by the liver called adropin. Animal models have shown that peptide hormones play an important role in regulating glucose levels and fatty acid metabolism and that irregular function of these hormones can have a direct effect on an individual's risk of developing obesity and/or diabetes.

"We were studying animal models of insulin resistance as precursor to type 2 diabetes, when we came across adropin," Butler said. "We found it provocative that this particular peptide hormone was distributed in the brain, liver, and pancreas—three tissues that are of great interest to those of us in the diabetes research field."

Butler noted that adropin seems to play a role in maintaining normal insulin sensitivity—whereby only a relatively small amount of insulin is needed to maintain regular blood glucose levels. In type 2 diabetes, insulin sensitivity is often blunted, which means that the normal amounts of insulin produced by the body are no longer as effective in lowering blood glucose levels.

"What has not been established are the mechanisms and sites of action that effect glucose homeostasis [equilibrium]," he said. "So that's what we're going to spend the next two years finding out with the help of this research grant from Novo Nordisk."

The research will also explore adropin's potential role as a protein-based therapy for treating type 2 diabetes, a chronic disease that affects over 300 million people worldwide, according to the World Health Organization. "Clearly, there is an urgent need to identify

new and more effective drugs for treating diabetes,” Butler said. “Studying how adropin works in this regard could eventually contribute to this effort.”

## **Scientist Awarded \$1 Million Grant to Develop New Tools for Hepatitis C Treatment Discovery**

Scientists from the Florida campus of The Scripps Research Institute have been awarded just over \$1 million from the National Institutes of Health for a three-year study to develop new high-throughput screening tests to find compounds that disable a protein essential to hepatitis C virus (HCV) replication.

Timothy Tellinghuisen, a Scripps Florida associate professor, is the principal investigator for the study.

Hepatitis C is a slow-progressing disease that causes inflammation of the liver and affects some 170 million people worldwide, according to the Hepatitis Foundation International. Like the current approach to HIV/AIDS, a cocktail-based therapeutic approach, which uses multiple inhibitors targeting distinct aspects of the HCV life cycle, has emerged as one of the most promising.

In the search for new treatments against HCV, it has become critical to develop novel targets to attack. Tellinghuisen's new research is focused on a potentially potent, but somewhat neglected, enzyme. This protease—an enzyme that breaks down proteins—is known as NS2, which is necessary for productive infections that produce new viruses and spread the infection among cells.

"The NS2 protein is needed for hepatitis C infections, but is poorly understood," Tellinghuisen said. "The new grant will help us develop potential chemical tools to look at the role of NS2 in HCV biology because we really don't know how the protein works."

Some recent studies suggest that the NS2 protease may be involved in altering gene expression in the host cell and in helping the virus defend against apoptosis or programmed cell death, in addition to the more direct roles for the protein in viral replication and particle assembly.

Tellinghuisen and his colleagues have already developed a small-scale screen to identify compounds that disrupt viral replication through NS2 protease activity.

"Our overall goal is to turn our small-scale NS2 assay into an assay appropriate for high-throughput small-molecule screening," he said, noting that would give the team access to the more expansive Molecular Libraries Probe Production Centers Network (MLPCN) screening center program at Scripps Florida.

MLPCN is a collaborative research network that uses use high-tech screening methods to identify small molecules to investigate the diverse functions of cells; Scripps Research is one of four large national centers.

### **Scientist Awarded \$1 Million for Stress-Associated Disease and Aging Research**

A scientist from the Florida campus of The Scripps Research Institute has been awarded just over \$1 million from the National Institutes of Health to develop a range of new tests that could lead to new treatments for a number of stress-associated and degenerative disorders of advancing age.

Shuji Kishi, an assistant professor at Scripps Research, is the principal investigator for the three-year study.

The new tests will focus on diseases linked to oxidative stress (and the stress-induced inflammation that often accompanies it), closely associated with aging. Those diseases include atherosclerosis, Alzheimer's and Parkinson's disease, diabetes, heart attack, sarcopenia, liver and kidney disease, and stroke.

Despite the widespread damage caused by oxidative stress, the number of therapeutic remedies for it remains virtually non-existent.

During periods of cellular stress, such as exposure to UV radiation or chronic diseases like cancer, the level of highly reactive oxygen-containing molecules in cells can increase, resulting in misfolded proteins and cell damage. Cells can protect themselves from this damage by activating certain antioxidant genes, but age and extended periods of stress can impair that response.

In the new study, Kishi plans to develop a series of tests to identify drug leads that will prevent oxidative damage in a novel vertebrate model. His approach will involve high-content screens in zebrafish.

"The cell-based assays can be pursued using the ultra-high-throughput screening resources available at Scripps Florida, including a chemical library comprised of approximately 1 million compounds with structures that we know have properties suitable for drug development," Kishi said.

Beyond the cell-based tests, Kishi plans to use newly developed transgenic zebrafish as a model organism for testing any drug candidates uncovered during cell-based screening. Those with potential after this round of testing will then be further evaluated to determine organ specificity and developmental toxicity, and for overall efficacy in preventing oxidative damage.



“We want to understand how these selected small molecules work in the zebrafish so that additional drugs can be designed based on the in vivo antioxidant response,” Kishi said.

Kishi’s laboratory is broadly focused on developing experimental models of aging and geriatric diseases, including neurodegenerative diseases.

### **Scripps Florida Scientist Awarded \$700,000 to Develop New Treatments for Cocaine Addiction**

A scientist on the Florida campus of The Scripps Research Institute has been awarded more than \$700,000 by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH), to study and optimize newly discovered compounds to combat cocaine addiction.

Thomas Bannister, an assistant professor in the Department of Chemistry and associate scientific director in the Translational Research Institute at Scripps Florida, is the principal investigator for the five-year study. Chemists in the Bannister group discovered the compounds as part of an effort to find new classes of molecules capable of treating brain disorders.

“Long-term drug addiction can cause biochemical changes in the brain of the drug user,” said Bannister. “Unfortunately the changes can reinforce the addiction, making it much more difficult to resist the urge to relapse. Animal studies suggest that there may be ways to normalize the brain chemistry of long-term drug users and raise the odds for a successful recovery.”

The Bannister lab’s hypothesis is that drugs capable of selective interactions with a brain protein called the NOP receptor will be beneficial in addiction therapy. The main hurdle in testing this hypothesis has been that drugs known to interact with the NOP receptor also interact with opioid receptors, where drugs such as morphine, Oxycontin®, and Vicoden® act to provide both pain relief and unwanted addictive effects. Thus if these drugs were used for treating cocaine addiction, they could simply cause a different addiction, a trade-off that wouldn’t be particularly useful.

The key finding prompting the grant application was new chemistry that gave molecules increased selectivity for the NOP receptor over the opioid receptors.

“We found molecules that were biologically specific, acting only at the NOP receptor and having no opiate effects,” said Bannister. “We made these advances while receiving funding from a NIH/NIDA one-year “economic stimulus” grant, in collaboration with Claes Wahlestedt and co-workers at the University of Miami. Claes’s group used studies with mice to show that our selective new compounds were not addictive. They also found that

drug-adapted mice, after taking one of our best lead molecules, consumed less cocaine than untreated mice.”

While many more studies are needed to see if such therapy can work in humans, the new grant represents a major step toward that objective.

“This grant will allow us to optimize the chemical and biological properties of these molecules and to extensively study their effects in the brain,” said Bannister. “The long-term goal is to develop an entirely new and effective method for treating cocaine addiction.”

## **Scripps Research Scientist Awarded \$500,000 Grant from Michael J. Fox Foundation to Study Parkinson Disease**

*Funding Could Help Uncover Novel Therapeutic Target for Neurodegenerative Disorder*

The Scripps Research Institute has been awarded a \$500,000 grant by the Michael J. Fox Foundation to study a pair of genetic mutations that could lead to a new and potentially vital therapeutic target for Parkinson’s disease, a progressive and fatal neurodegenerative disorder.

Philip LoGrasso, PhD, a professor in molecular therapeutics and senior director for drug discovery at Scripps Florida, is the principal investigator for the project.

The study will focus on two genes, the leucine-rich repeat kinase 2 (LRRK2) and the serum glucocorticoid-regulated kinase 1 (SGK1). Genetic testing of several thousand Parkinson’s patients has shown that the risk of Parkinson’s disease associated with mutations in the LRRK2 gene are substantially reduced by mutations in the SGK1 genes, bringing the risk back in line with that of the general population.

“As a kinase, LRRK2 is the kind of molecule that drugmakers have a great deal of experience targeting. And as a significant genetic contributor to Parkinson’s disease, it provides important therapeutic avenues for understanding the biological mechanisms and clinical aspects of PD,” said Todd Sherer, PhD, CEO of The Michael J. Fox Foundation. “Dr. LoGrasso’s expertise in kinases and his well known work in developing novel treatments for Parkinson’s disease will be a particularly valuable addition to the promising research already being carried out with funding from the Foundation.”

SGK1 was discovered by 23andMe, Inc., a leading personal genetics company. The company currently has 125,000 genotyped customers, and nearly 90 percent have opted-in to participate in the company’s Institutional Review Board-approved research. 23andMe has amassed the single largest Parkinson’s research cohort in the world, which now comprises

approximately 6,000 participants and includes one of the largest cohorts of individuals carrying the pathogenic mutations in the LRRK2 gene.

With this award Dr. LoGrasso joins the LRRK2 Consortium, established last year by the Michael J. Fox Foundation. The consortium is an international group of academic and industry partners dedicated to accelerating LRRK2 therapeutic development.

“I want to thank the Fox Foundation for their generous grant,” LoGrasso said, “and for giving me the opportunity to study the links between these intriguing genetic mutations. The question our laboratory will explore is how SGK1 works and how it impacts the LRRK2 mutation. We’re all hoping that ultimately this produces a new target for treatment intervention – because there are no viable long-term treatments available today.”

Since the 1960s the mainstay for the treatment of Parkinson’s disease has been levodopa (L-DOPA), a drug that provides only symptomatic relief. Unfortunately, L-DOPA loses efficacy over time and has numerous side effects that limit its effectiveness.

Patients with Parkinson’s disease suffer from a loss of dopaminergic neurons in a specific area of the brain. An estimated one million Americans are believed to suffer from the disease, according to the Parkinson’s Disease Foundation; approximately 40,000 new cases are reported annually.

The LRRK2 gene was first linked to Parkinson’s disease in 2004, and many believe it to be the most common genetic contributing factor to the disease. While hereditary forms of the disease are relatively rare – an estimated five to 10 percent – unlocking the mechanisms involved in both LRRK2 and SGK1 could eventually benefit all patients.

Mutations in the LRRK2 gene have been linked with an increased risk not only of Parkinson’s disease, but also of Crohn’s disease. SGK1 is involved in a number of biomolecular processes including inflammation, cell proliferation, and apoptosis or programmed cell death. It is believed that the gene also plays a role in brain disorders other than Parkinson’s disease, such as schizophrenia, depression, and Alzheimer’s disease.

### **Scientist Wins Pair of Grants to Study Critical Component of Memory**

Sathyanaryanan Puthanveetil, an assistant professor on the Florida campus of The Scripps Research Institute, has been awarded a pair of notable grants to study a critical component of long-term memory formation.

Puthanveetil will receive \$225,000 over three years from the prestigious Whitehall Foundation to study the role in long-term memory of a motor protein called kinesin. In this study, he will use the marine snail, *Aplysia*, a favorite of memory researchers because of its exceptionally large neurons and simple nervous system.

In addition to the Whitehall award, Puthanveettil has received a one-year, \$100,000 grant from the Alzheimer's Drug Discovery Foundation. Puthanveettil also plans to use the award to study kinesin, in this case to develop molecular screens to identify small molecules that can modulate kinesin function in the mammalian brain. This work will be conducted in collaboration with Scripps Research colleagues Peter Hodder, senior scientific director of lead identification, and William Roush, chemistry professor, executive director of Medicinal Chemistry, and associate dean of graduate studies at Scripps Florida.

"To be selected for an award by the Whitehall Foundation is a great honor," Puthanveettil said. "I'm also delighted with the grant from the Alzheimer's Drug Discovery Foundation, another important institution that supports the search for new therapeutics. Both awards will help advance my research substantially."

Puthanveettil has long been interested in axonal transport and its role in the molecular mechanisms underlying long-term memory storage, in particular the cellular transport of various gene products such as proteins and RNAs in the brain.

In a 2008 study published in the journal *Cell*, Puthanveettil showed for the first time that the induction of long-term facilitation—the cellular basis of memory and learning involving enhancement of communication between neurons—requires upregulation of specific isoform of kinesin.

Ultimately, he hopes his research will lead to an understanding of the basic pathology of various neurological disorders.

"For example, in the case of Huntington's disease, kinesin is responsible for transport of molecules that play a role in the disease," he said. "We want to know how the transport of these molecules is modified during the disease's development. Likewise for Alzheimer's disease—if you can find a way to manipulate the transport system, you may be able to overcome some of the defects involved in the disease's pathology."

### **Scripps Research Licenses New Instrumentation Platform That Dramatically Improves Compound Management**

Scientists from the Florida campus of The Scripps Research Institute have designed and licensed a major new technology that dramatically improves the quality control and management of compounds used for high-throughput screening, a process that can be used to search for potential new drugs.

The technology, which consists of an automated instrumentation platform called the Plate Auditor™, has been licensed for manufacture and sale to the Brooks Life Science Systems division of Brooks Automation, a leading worldwide provider of automation, vacuum, and

instrumentation solutions for multiple markets including semiconductor manufacturing, life sciences, and clean energy.

The Plate Auditor™ was designed by Peter Hodder, senior scientific director, and his laboratory staff, Louis Scampavia and Pierre Baillargeon. It combines advanced spectroscopy and image analysis techniques to perform rapid, automated, and nondestructive quality assessment of compounds in high-throughput screening collections. It also monitors the quality of all samples through their lifecycle, a practice not currently possible with existing technologies.

“This is the first instrument of its kind and first in its class,” Hodder said. “As a detection platform, it provides a wealth of information about a compound sample that you simply couldn’t get from one instrument.”

Scripps Research uses the instrument routinely for quality control of more than 1 million compounds in its drug-discovery screening operation.

John Lillig, senior vice president and managing director of Brooks Life Science Systems, commented, “As the leader in providing automated compound and biological sample management systems to pharmaceutical and biotech companies around the world, Brooks is very excited to be working together with the Scripps Research Institute’s Compound Management Group on the development and the commercialization of this innovative and very useful Compound/HTS Quality Assurance technology. With over 350 million samples stored in Brooks Sample Management Systems around the world, the new Scripps Research/Brooks Plate Auditor™ will be a very nice complement to our Brooks Tube Auditor™ product offering and a valuable new quality enhancement tool for our many Compound Management colleagues around the world.”

The new instrument will debut at the First Annual Society for Laboratory Automation and Screening (SLAS) in February in San Diego, CA. Hodder himself will be presenting the new HI-API-CM at a European Lab Automation Conference this May.

Hodder hopes the new technology gets people thinking about Scripps Florida in a brand new way.

“We want people to know that in addition to discovering therapeutic molecules, we can also design and build novel instrumentation for screening operations,” said Hodder, who founded and has directed the high-throughput screening laboratory at Scripps Florida since 2005.

More information on the technology can be found in a recent publication, “Monitoring of HTS compound library quality via a high-resolution image acquisition and processing instrument, by Baillargeon P., Scampavia L., Einsteder R., and Hodder P. in the *Journal of Laboratory Automation* 2011 Jun;16(3):197-203) or the technology patent (<http://www.wipo.int/patentscope/search/en/WO2010057081>)

## **Scripps Research Institute and OPKO Health Announce Global License Agreement for a Novel Compound That Blocks Brain Cell Destruction in Parkinson's Disease**

The Scripps Research Institute and OPKO Health, Inc. (NYSE: OPK) today announced a global agreement for the development and commercialization of SR 3306, a novel compound discovered by scientists from the Florida campus of The Scripps Research Institute that blocks the destruction of brains cells in animal models of Parkinson's disease.

"This licensing agreement will help insure that the development of this promising compound keeps moving forward," said Scripps Research Professor Philip LoGrasso, Ph.D., whose laboratory has led the research on the compound to date. "This is one of the best opportunities we have for the development of an effective neuroprotective treatment for Parkinson's patients."

Under the terms of the agreement, Scripps Research has granted to OPKO Health exclusive worldwide rights to develop, manufacture, and commercialize SR 3306 and related compounds that inhibit a class of enzymes called jun-N-terminal kinsases (JNK) that play an important role in neuron survival. The new compound would potentially be the first to protect the brain from the ravages of Parkinson's disease.

"We are excited to be working with Dr. LoGrasso and The Scripps Research Institute to develop this important compound which could prevent the progression of Parkinson's disease and not just treat the symptoms of the disease," said Phillip Frost, M.D., Chairman and Chief Executive Officer of OPKO.

Parkinson's disease, a degenerative neurological disorder that reduces the brain's ability to produce dopamine, affects about 1 million Americans. Currently prescribed drugs for Parkinson's disease—including levodopa and so-called MAO-B inhibitors—can counteract symptoms of the disease but not stop its progression.

The LoGrasso lab described SR-3306 in a pair of studies published in February 2011 in the journal *ACS Chemical Neuroscience*.

### **Part 3: Scientific Accomplishments**

#### **Scripps Research Scientists Develop Brand New Class of Small Molecules through Innovative Chemistry**

*Novel Approach Could Greatly Expand, Accelerate Drug Discovery Process*

Inspired by natural products, scientists on the Florida campus of The Scripps Research Institute have created a new class of small molecules with the potential to serve as a rich foundation for drug discovery.

Combining the power of synthetic chemistry with some advanced screening technologies, the new approach could eventually expand by millions the number of provocative synthetic compounds available to explore as potential drug candidates. This approach overcomes substantial molecular limitations associated with state-of-the-art approaches in small molecule synthesis and screening, which often serve as the foundation of current drug discovery efforts.

The study, led by Scripps Research Associate Professor Glenn Micalizio, was published November 20, 2011, in an advanced online edition of the journal *Nature Chemistry*.

To frame the significance of this advance, Micalizio explains that high-throughput screening is an important component of modern drug discovery. In high-throughput screening, diverse collections of molecules are evaluated en masse for potential function in a biological area of interest. In this process, success is critically dependent on the composition of the molecular collections under evaluation. Modern screening centers maintain a relatively static collection of molecules, the majority of which are commercially available materials that have structures unrelated to natural products—molecules that are appreciated as validated leads for drug development.

“This divergence in structure between natural products and commercially available synthetics lies at the heart of our inquiry,” said Micalizio. “Why should we limit discovery of therapeutic leads to compound collections that are influenced by concerns relating to commercial availability and compatibility with an artificial set of constraints associated with the structure of modern screening centers?”

To expand the compounds available for investigation, the scientists embraced an approach to structural diversity that mimics nature’s engine for the discovery of molecules with biological function. This process, termed “oligomerization,” is a modular means of assembling structures (akin to the way that letters are used in a sequence to provide words with meaning) where a small collection of monomeric units can deliver a vast collection of oligomeric products of varying length, structure, and function (like the diversity of words presented in a dictionary).

Coupling this technique with a synthetic design aimed at generating molecules that boast molecular features inspired by the structures of bioactive natural products (specifically, polyketide-derived natural products, which include erythromycin, FK-506, and epothilone), the scientists established a new chemical platform for the discovery of potential therapeutics.

Micalizio points out: “The importance of oligomerization to drive discovery is well appreciated in chemistry and biology, yet a means to realize this process as an entry to small molecule natural product-inspired structures has remained elusive. The crux of the

problem is related to challenges associated with the control of shape for each member of a complex oligomer collection—the central molecular feature that defines biological function.”

“It is the stability associated with the shape of these new compounds that lies at the heart of the practical advance,” he continued. “The unique features of this science now make possible the ability to synthesize large collections of diverse natural product-inspired structures that have predictable and stable three-dimensional shapes.”

Micalizio said that the science described represents a first step toward revolutionizing discovery at the interface of chemistry, biology, and medicine by embracing nature’s strategy for molecular discovery. Coupling this type of advance with modern screening technology that can handle the evaluation of large compound collections at low cost (such as work by Scripps Florida Professor Thomas Kodadek, a co-author of the new study), can dramatically enhance the future of pharmaceutically relevant science.

The potential of this vision was highlighted in the new study, in which a 160,000-member compound collection was employed to discover the first non-covalent small molecule ligand to the DNA binding domain of p53—an important transcription factor that regulates a variety of genes involved in cell cycle control and cell death.

The first author of the study, “A Biomimetic Polyketide-Inspired Approach to Small-Molecule Ligand Discovery,” is Claudio Aquino of Scripps Research. In addition to Micalizio and Kodadek, other authors include Mohosin Sarkar, Michael J. Chalmers, and Kimberly Mendes.

The study was supported by the Fidelity Biosciences Research Initiative, The State of Florida (The Florida Funding Corporation), and the National Institutes of Health.

## **Scripps Research Scientists Uncover New Role for Gene in Maintaining Steady Weight**

### *The Findings May Help Scientists Combat Obesity and Diabetes*

Against the backdrop of the growing epidemic of obesity in the United States, scientists from the Florida campus of The Scripps Research Institute have made an important new discovery regarding a specific gene that plays an important role in keeping a steady balance between our food intake and energy expenditure. The study may help scientists better understand the keys to fighting obesity and related disorders such as diabetes.

The study, which was published in the November 25, 2011 print edition of *The Journal of Biological Chemistry*, focused on the melanocortin-3 receptor (MC3R), which normally responds to signals of nutrient intake.



“What we discovered was quite a surprise,” said Scripps Research Associate Professor Andrew Butler, who led the study. “We thought that the actions of the receptor expressed in the brain would be critical for metabolic homeostasis. However, what we found is that actions of the receptor expressed outside the brain appear to be equally important.”

The existence of drug targets in areas outside of the central nervous system (the body’s “periphery”) might help in the effort to develop drugs that influence metabolism without major side effects, Butler said.

The findings were made possible by the team’s development of a new transgenic animal model, where expression of the MC3R gene can be selectively “switched on” in different cell types.

In the study, the suppression of MC3R expression in the brain and peripheral tissues had a marked impact on metabolic homeostasis (equilibrium). Interestingly, mice expressing the MC3R gene in the brain only displayed an obese phenotype (physical appearance) similar to those where all types of expression was suppressed, indicating that actions of this receptor in the brain are not sufficient to protect against weight gain. The finding that loss of MC3R activity in the periphery impairs metabolic homeostasis is startling, Butler said, and point to a distinct role for MC3R signaling in the peripheral tissues. However, how the actions of these receptors impacts on obesity remains to be determined.

“It’s clear that these peripheral receptors are important and the new mouse model will let us explore that potential,” Butler said.

The first author of the study, “Genetic dissection of melanocortin-3 receptor function suggests roles for central and peripheral receptors in energy homeostasis,” is Karima Begriche of Scripps Research. In addition to Butler and Begriche, other authors include Jari Rossi, Danielle Skorupa, Laura A. Solt, Brandon Young, and Thomas P. Burris from The Scripps Research Institute in Florida; Randall L. Mynatt and Jingying Zhang at the Pennington Biomedical Research Center, which is part of the Louisiana State University System; and Peter R. Levasseur and Daniel L. Marks at the Oregon Health & Science University. See

<http://www.jbc.org/content/early/2011/10/07/jbc.M111.278374.abstract?sid=8a17ce75-de95-45d1-b688-a039da52b5f1>

The study was supported by National Institutes of Health and the Pennington Biomedical Research Foundation.

## **Scripps Research Scientists Elevate Little-Studied Cellular Mechanism to Potential Drug Target**

For years, science has generally considered the phosphorylation of proteins—the insertion of a phosphorous group into a protein that turns it on or off—as perhaps the factor

regulating a range of cellular processes from cell metabolism to programmed cell death. Now, scientists from the Florida campus of The Scripps Research Institute have identified the importance of a novel protein-regulating mechanism—called sulfenylation—that is similar to phosphorylation and may, in fact, open up opportunities to develop new types of drugs for diseases such as cancer.

The study was published December 11, 2011, in an advance online edition of the journal *Nature Chemical Biology*.

“With this paper, we’ve elevated protein sulfenylation from a marker of oxidative stress to a bona fide reversible post translational modification that plays a key regulatory role during cell signaling,” said Kate Carroll, a Scripps Research associate professor who led the study. “The sulfenyl modification is the new kid on the block.”

During periods of cellular stress, caused by factors such as exposure to UV radiation or chronic disease states like cancer, the level of highly reactive oxygen-containing molecules can increase, resulting in inappropriate modification of proteins and cell damage. In sulfenylation, one oxidant, hydrogen peroxide, functions as a messenger that can activate cell proliferation through oxidation of cysteine residues in signaling proteins, producing sulfenic acid. Cysteine, an amino acid (natural protein building block), is highly oxidant sensitive.

Conventional wisdom has long held that if hydrogen peroxide does exist in the cell at any appreciable level, it represents a disease state, not a regulatory event. The new study shows that sulfenylation is actually a positive protein modification, and that it’s required for signaling through the pathway, a validation of a long-held belief in some scientific circles that hydrogen peroxide functions as a general signaling molecule, not an oxidative “bad boy” to be eliminated at all costs.

#### *A New Chemical Probe*

To explore the process, Carroll and her colleagues developed a highly selective chemical probe—known as DYn-2—with the ability to detect minute differences in sulfenylation rates within the cell.

With the new probe, the team was able to show that a key signaling protein, epidermal growth factor receptor (EGFR), is directly modified by hydrogen peroxide at a critical active site cysteine, stimulating its tyrosine kinase activity.

The technology described in the new paper is unique, Carroll said, because it allows scientists to trap and detect these modifications in situ, without interfering with the redox balance of the cell. “Probing cysteine oxidation in a cell lysate is like looking for a needle in a haystack,” she said, “our new approach preserves labile sulfenyl modifications and avoids protein oxidation artifacts that arise during cell homogenization.”

As with phosphorylation, future studies on sulfenylation will delve into the exciting discovery of new enzymes, new signaling processes, and new mechanisms of regulation.

Another broad impact of these findings, Carroll said, is to open up an entirely new mechanism to exploit for the development of therapeutics, particularly in cancer.

“It should influence the design of inhibitors that target oxidant-sensitive cysteine residues in the future,” she said.

The first author of the study, “Peroxide-dependent Sulfenylation of the EGFR Catalytic Site Enhances Kinase Activity,” is Candice E. Paulsen of the University of Michigan. Other authors include Thu H. Truong and Stephen E. Leonard of the University of Michigan; and Francisco J. Garcia, Arne Homann and Vinayak Gupta of Scripps Research.

The study was supported by the Camille Henry Dreyfus Teacher Scholar Award and the American Heart Association.

## **Scripps Research Scientists Paint New Picture of Dance Between Protein and Binding Partners**

### *New Findings Could Influence Design of Future Diabetes Treatments*

Using a blend of technologies, scientists from the Florida campus of The Scripps Research Institute have painted a new picture of how biochemical information can be transmitted through the modification of a protein.

Previously, scientists believed that during the pairing of proteins and their binding partners (“ligands”), proteins modified their shape while ligands remained stable. The new study shows this one-size-fits-all solution is not entirely accurate.

Instead, the situation resembles a kind of complex but carefully organized dance routine, where the ligand samples a variety of binding modes while the protein also modifies its shape, a process that results in their pairing and changes in the protein critical for its function.

These new findings, published in the January 11, 2012 edition of the journal *Structure*, could affect future drug design.

“Using a multidisciplinary approach, we gleaned something from our data that no one else has,” said Douglas Kojetin, an assistant professor on the Scripps Florida campus who led the study. “The conventional wisdom is that ligands bind in one orientation but our study shows that they can bind in multiple modes. That means if we can optimize a ligand to bind in mode B rather than mode A, we might be able to select the therapeutic results we want.”

The new study—which used a number of complementary technologies including NMR spectroscopy and hydrogen/deuterium exchange (HDX) coupled to mass spectrometry, combined with previous x-ray crystallography analyses—provides detailed insights into the real-time actions of molecules that could never be determined with a single technology.

Specifically, the researchers revealed insights into ligand and receptor dynamics in the nuclear receptor known as PPAR $\gamma$  (peroxisome-proliferator-activated receptor). PPAR $\gamma$  has been implicated in metabolic diseases including obesity, diabetes, and atherosclerosis.

The study also found that various gradations in these ligands influence the dynamics of this exchange, adding another layer of complexity. “One of the compounds, MRL24, binds to the receptor and has anti-diabetic efficacy, but doesn’t activate it very well,” Kojetin said. “This is what you want because when the receptor is activated you get side effects such as weight gain and brittle bones.”

“This study in particular highlights the importance of multidisciplinary collaborative efforts to truly understand the molecular details of drug-receptor interactions”, says Kojetin. “This work is an excellent example of the strong campus collaborations we have with the laboratories of Patrick Griffin, Thomas Burris, and Theodore Kamenecka.”

The first author of the study, “Ligand and Receptor Dynamics Contribute to the Mechanism of Graded PPAR  $\gamma$  Agonism,” is Travis S. Hughes of Scripps Research. Other authors include Michael J. Chalmers, Scott Novick, Dana S. Kuruvilla, Mi Ra Chang, Theodore M. Kamenecka, Thomas P. Burris, and Patrick R. Griffin of Scripps Research; Mark Rance of the University of Cincinnati; and Bruce A. Johnson of One Moon Scientific Inc.

The study was supported by the James and Esther King Biomedical Research Program, Florida Department of Health start up funds for Scripps Research, the National Institutes of Health, and the National Center for Research Resources.

## **Scripps Research Scientists Create Novel RNA Repair Technology**

*Discovery Could Aid Search for Huntington’s, Spinocerebellar Ataxia, and Kennedy Disease Treatments*

Scientists from the Florida campus of The Scripps Research Institute have identified a compound that can help repair a specific type of defect in RNA, a type of genetic material. The methods in the new study could accelerate the development of therapeutics to treat a variety of incurable diseases such as Huntington’s disease, Spinocerebellar ataxia, and Kennedy disease.

The new study, published January 17, 2012 in an advance, online edition of the journal *ACS Chemical Biology*, describes a method to find compounds that target defective RNAs, specifically RNA that carries a structural motif known as an “expanded triplet repeat.” The

triplet repeat, a series of three nucleotides repeated many more times than normal in the genetic code of affected individuals, has been associated with a variety of neurological and neuromuscular disorders.

“For a long time it was thought that only the protein translated from this type of RNA was toxic,” said Matthew Disney, an associate professor at Scripps Florida who led the new study. “But it has been shown recently that both the protein and the RNA are toxic. Our discovery of a small molecule that binds to RNA and shuts off its toxicity not only further demonstrates that the RNA is toxic but also opens up new avenues for therapeutic development because we have clearly demonstrated that small molecules can reverse this type of defect.”

In the new research, the scientists used a query molecule called 4', 6-diamidino-2-phenylindole (DAPI) as a chemical and structural template to find similar but more active compounds to inhibit a toxic CAG triplet repeat. One of these compounds was then found effective in inhibiting the RNS toxicity of the repeat in patient-derived cells, which demonstrated an improvement in early-stage abnormalities.

“The toxic RNA defect actually sucks up other proteins that play critical roles in RNA processing, and that is what contributes to these various diseases,” Disney said. “Our new compound targets the toxic RNA and inhibits protein binding, shutting off the toxicity. Since the development of drugs that target RNA is extremely challenging, these studies can open up new avenues to exploit RNA drug targets that cause a host of other RNA-mediated diseases.”

Disney and his colleagues are already hard at work to extend the lab’s findings.

The lead author of the study, “Chemical Correction of Pre-mRNA Splicing Defects Associated with Sequestration of Muscleblind-Like 1 Protein by Expanded r(CAG)-containing Transcripts,” is Amit Kumar of Scripps Research. Other authors include Raman Parkesh and Jessica Childs-Disney of Scripps Research, and Lukasz J. Sznajder and Krzysztof Sobczak of Adam Mickiewicz University, Poland. For more information, see <http://pubs.acs.org/doi/abs/10.1021/cb200413a>

The study was supported by the National Institutes of Health and the Polish Ministry of Science and Higher Education, Camille & Henry Dreyfus Foundation, and the Research Corporation for Science Advancement.

## **An Intriguing Combination in the Brain May Modify Our Appetites, Alter Other Key Processes**

*Finding Paves the Way for New Therapies*

The interaction between a disparate pair of brain proteins may have a profound effect on the regulation of appetite, according to a new study by scientists from the Florida campus of The Scripps Research Institute. The complex partnership may also have an impact on other signaling pathways linked to neuropsychiatric disorders as wide-ranging as Parkinson's disease, schizophrenia, and addiction.

“Our findings provide new insights into the way the body regulates appetite and other processes,” said Roy G. Smith, chair of the Scripps Research Department of Metabolism and Aging, who authored the new study with Staff Scientist Andras Kern and other Scripps Research colleagues. “The work provides exciting opportunities for designing next generation therapeutics with fewer side effects for both obesity and psychiatric disorders associated with abnormal dopamine signaling.”

The study, published in the most recent issue of the journal *Neuron*, reveals a fascinating partnership within the brain neurons that regulate appetite, a unique complex of hormone and neurotransmitter receptors that no one suspected existed before the new research.

One of these is the receptor for ghrelin (GHSR1a), a small peptide hormone that is produced mainly in the stomach. As an evolutionary warning signal that promotes weight gain and fat during periods of weight loss, ghrelin can be blamed for the failure of most modern diets.

The other key player is the dopamine receptor known as subtype-2 (DRD2), part of the dopamine signaling pathway. Dopamine is a neurotransmitter that plays a key role in the brain's reward centers, and can lead to pleasure producing behavior, such as drug abuse and overeating.

The study identifies this twin receptor complex, which is naturally present in the brain's neurons that regulate appetite, and sheds light on its role in modifying dopamine signaling.

“We were able to show there are subsets of brain neurons that express both the ghrelin receptor and the dopamine receptor subtype-2,” Smith said.

The study went on to show that when these two receptors are co-expressed, the receptors physically interact with each other, which leads to an alteration of dopamine signaling. And when mice were treated with a molecule (cabergoline) that selectively activates the dopamine receptor, they lost weight. Interestingly, cabergoline-stimulated weight loss did not require ghrelin, but was dependent on the receptor for ghrelin and its interaction with the dopamine receptor.

In addition, cabergoline blocked dopamine signaling only for the complex—a fact that Smith finds promising. “This allows for neuronal selective fine-tuning of dopamine signaling because neurons expressing only the dopamine receptor will be unaffected,” he said.

In addition to Smith and Kern, authors of the paper, “Apo-Ghrelin Receptor forms Heteromers with DRD2 in Hypothalamic Neurons and is Essential for Anorexigenic Effects of DRD2 Agonism,” are Rosie Albarran-Zeckler and Heidi E. Walsh of Scripps Research. For more information, see [http://www.cell.com/neuron/fulltext/S0896-6273\(11\)01087-7](http://www.cell.com/neuron/fulltext/S0896-6273(11)01087-7)

The study was supported by The National Institutes of Health.

## **Scripps Research Scientists Identify Most Lethal Known Species of Prion Protein**

*Findings Suggest New View of “Mad Cow” and Other Neurodegenerative Diseases*

Scientists from the Florida campus of The Scripps Research Institute have identified a single prion protein that causes neuronal death similar to that seen in “mad cow” disease, but is at least 10 times more lethal than larger prion species.

This toxic single molecule or “monomer” challenges the prevailing concept that neuronal damage is linked to the toxicity of prion protein aggregates called “oligomers.”

The study was published this week in an advance, online edition of the journal *Proceedings of the National Academy of Sciences*.

“By identifying a single molecule as the most toxic species of prion proteins, we’ve opened a new chapter in understanding how prion-induced neurodegeneration occurs,” said Scripps Florida Professor Corinne Lasmézas, who led the new study. “We didn’t think we would find neuronal death from this toxic monomer so close to what normally happens in the disease state. Now we have a powerful tool to explore the mechanisms of neurodegeneration.”

In the study, the newly identified toxic form of abnormal prion protein, known as TPrP, caused several forms of neuronal damage ranging from apoptosis (programmed cell death) to autophagy, the self-eating of cellular components, as well as molecular signatures remarkably similar to that observed in the brains of prion-infected animals. The study found the most toxic form of prion protein was a specific structure known as alpha-helical.

### *New Paths to Explore*

In addition to the insights it offers into prion diseases such as “mad cow” and a rare human form Creutzfeldt-Jakob disease, the study opens the possibility that similar neurotoxic proteins might be involved in neurodegenerative disorders such as Alzheimer’s and Parkinson diseases.

In prion disease, infectious prions (short for proteinaceous infectious particles), thought to be composed solely of protein, have the ability to reproduce, despite the fact that they lack DNA and RNA. Mammalian cells normally produce what is known as cellular prion protein

or PrP; during infection with a prion disease, the abnormal or misfolded protein converts the normal host prion protein into its disease form.

Lasmézas explains that prion diseases are similar to Alzheimer's and other protein misfolding diseases in that they are caused by the toxicity of a misfolded host protein. Recent work, as reported in *The New York Times*, also found that diseases such as Alzheimer's resemble prion diseases by spreading from cell to cell.

The new study adds another twist. "Until now, it was thought that oligomers of proteins are toxic in all these diseases," Lasmézas said. "Since we found for the first time that an abnormally folded monomer is highly toxic, it opens up the possibility that this might be true also for some other protein misfolding diseases as well."

The first author of the study, "Highly Neurotoxic Monomeric  $\alpha$ -Helical Prion Protein," is Minghai Zhou of Scripps Research. Other authors include Gregory Ottenberg and Gian Franco Sferrazza also of Scripps Research. For more information on the study, see <http://www.pnas.org/content/early/2012/02/07/1118090109.abstract>

The study was supported by the State of Florida.

## **Scripps Research Scientists Create Potent Molecules Aimed at Treating Muscular Dystrophy**

*The new approach could have implications for many genetic diseases*

While RNA is an appealing drug target, small molecules that can actually affect its function have rarely been found. But now scientists from the Florida campus of The Scripps Research Institute have for the first time designed a series of small molecules that act against an RNA defect directly responsible for the most common form of adult-onset muscular dystrophy.

In two related studies published recently in online-before-print editions of *Journal of the American Chemical Society* and *ACS Chemical Biology*, the scientists show that these novel compounds significantly improve a number of biological defects associated with myotonic dystrophy type 1 in both cell culture and animal models.

"Our compounds attack the root cause of the disease and they improve defects in animal models," said Scripps Research Associate Professor Matthew Disney, PhD. "This represents a significant advance in rational design of compounds targeting RNA. The work not only opens up potential therapies for this type of muscular dystrophy, but also paves the way for RNA-targeted therapeutics in general."

Myotonic dystrophy type 1 involves a type of RNA defect known as a "triplet repeat," a series of three nucleotides repeated more times than normal in an individual's genetic



code. In this case, the repetition of the cytosine-uracil-guanine (CUG) in RNA sequence leads to disease by binding to a particular protein, MBNL1, rendering it inactive. This results in a number of protein splicing abnormalities. Symptoms of this variable disease can include wasting of the muscles and other muscle problems, cataracts, heart defects, and hormone changes.

To find compounds that acted against the problematic RNA in the disease, Disney and his colleagues used information contained in an RNA motif-small molecule database that the group has been developing. By querying the database against the secondary structure of the triplet repeat that causes myotonic dystrophy type 1, a lead compound targeting this RNA was quickly identified. The lead compounds were then custom-assembled to target the expanded repeat or further optimized using computational chemistry. In animal models, one of these compounds improved protein-splicing defects by more than 40 percent.

“There are limitless RNA targets involved in disease; the question is how to find small molecules that bind to them,” Disney said. “We’ve answered that question by rationally designing these compounds that target this RNA. There’s no reason that other bioactive small molecules targeting other RNAs couldn’t be developed using a similar approach.”

The first authors of the JACS study, “Design of a Bioactive Small Molecule that Targets the Myotonic Dystrophy Type 1 RNA via an RNA Motif-Ligand Database & Chemical Similarity Searching” (<http://pubs.acs.org/doi/abs/10.1021/ja210088v>), are Raman Parkesh and Jessica Childs-Disney of Scripps Research. Other authors include Amit Kumar and Tuan Tran also of Scripps Research; Masayuki Nakamori, Jason Hoskins and Charles A. Thornton of the University of Rochester; and Eric Wang, Thomas Wang and David Housman of the Massachusetts Institute of Technology. This study was supported by the National Institutes of Health, Scripps Research, the Camille & Henry Dreyfus Foundation, and the Research Corporation for Science Advancement.

The first author of the ACS Chemical Biology study, “Rationally Designed Small Molecules Targeting the RNA That Causes Myotonic Dystrophy Type 1 Are Potently Bioactive” (<http://pubs.acs.org/doi/abs/10.1021/cb200408a>) is Jessica L. Childs-Disney of Scripps Research. Other authors include Suzanne G. Rzuczek of Scripps Research and Jason Hoskins and Charles A. Thornton of the University of Rochester. This study was supported by the National Institutes of Health, the Muscular Dystrophy Association, Scripps Research, the Camille & Henry Dreyfus Foundation, and the Research Corporation for Science Advancement.

## **Scripps Florida Scientists Uncover Inflammatory Circuit That Triggers Breast Cancer**

*Findings Point to Potentially Effective New Therapeutic Target for Cancer Treatment and Prevention*

Although it's widely accepted that inflammation is a critical underlying factor in a range of diseases, including the progression of cancer, little is known about its role when normal cells become tumor cells. Now, scientists from the Florida campus of The Scripps Research Institute have shed new light on exactly how the activation of a pair of inflammatory signaling pathways leads to the transformation of normal breast cells to cancer cells.

The study, led by Jun-Li Luo, an assistant professor at Scripps Florida, was published online before print by the journal *Molecular Cell* on February 23, 2012.

The scientists' discovery points to the activation of a self-sustaining signaling circuit that inhibits a specific RNA, a well-known tumor suppressor that helps limit the spread of cancer (metastasis). Therapies that disable this circuit and halt this miRNA repression could have the potential to treat cancer.

### *The Spark that Ignites Trouble*

In the new study, scientists identified the specific pathways that transform breast epithelial cells into active cancer cells.

The researchers found immune/inflammatory cells ignite the transient activation of MEK/ERK and IKK/NF- $\kappa$ B pathways; the MEK/ERK pathway then directs a consistent activation of a signaling circuit in transformed cells. This consistent signaling circuit maintains the malignant state of the tumor cells.

Luo compares this process to starting a car—a car battery starts the engine much like the transient signal activation turns on the consistent signal circuit. Once the engine is started, it no longer needs the battery.

The scientists go on to show that the initial activation of these pathways also activates IL6, a cytokine involved in a number of inflammatory and autoimmune diseases, including cancer. IL6 acts as a tumor initiator, sparking the self-sustaining circuit in normal breast cells necessary for the initiation and maintenance of their transformed malignant state.

In establishing that self-sustaining signal circuit, IL6 represses the action of microRNA-200c, which is responsible for holding down inflammation and cell transformation. Since enhanced microRNA-200c expression impairs the growth of existing cancer cells and increases their sensitivity to anti-tumor drugs, compounds that disable microRNA-200c repression have the potential to act as a broad-spectrum therapeutic.

Interestingly, the new findings dovetail with the "multiple-hits theory" of tumor formation, which posits that once normal cells in the human body accumulate enough pre-cancerous mutations, they are at high-risk for transformation into tumor cells. While the newly described initial pathway activation is momentary and not enough to cause any lasting changes in cell behavior, it may be just enough to tip the cell's transformation to cancer, especially if it comes on top of an accumulation of other cellular changes.

The first author of the study, “IL6-Mediated Suppression of Mir-200c Directs Constitutive Activation of an Inflammatory Signaling Circuit That Drives Transformation and Tumorigenesis,” is Matjaz Rokavec of Scripps Research. Other authors include Weilin Wu, also of Scripps Research.

The study was supported by the National Institute of Health, the United States Department of Defense, the Florida Department of Health, and Frenchman’s Creek Women for Cancer Research.

### **Scripps Research Institute Scientists Create Compounds that Dramatically Alter Biological Clock and Lead to Weight Loss**

*The New Molecules Could Lead to Unique Treatments for Obesity, Diabetes, High Cholesterol, and Sleep Disorders*

Scientists from the Florida campus of The Scripps Research Institute have synthesized a pair of small molecules that dramatically alter the core biological clock in animal models, highlighting the compounds’ potential effectiveness in treating a remarkable range of disorders—including obesity, diabetes, high cholesterol, and serious sleep disorders.

The study was published on March 29, 2012, in an advance, online edition of the journal *Nature*.

The study showed that when administered in animal models the synthetic small molecules altered circadian rhythm and the pattern of core clock gene expression in the brain’s hypothalamus, the site of the master cellular clock that synchronizes daily rhythms in mammals; circadian rhythms are the physiological processes that respond to a 24-hour cycle of light and dark and are present in most living things.

When given to diet-induced obese mice, these same small molecules decreased obesity by reducing fat mass and markedly improving cholesterol levels and hyperglycemia—chronically high blood sugar levels that frequently lead to diabetes.

“The idea behind this research is that our circadian rhythms are coupled with metabolic processes and that you can modulate them pharmacologically,” said Thomas Burris, a professor at Scripps Florida who led the study. “As it turns out, the effect of that modulation is surprisingly positive—everything has been beneficial so far.”

Burris stressed that these compounds were first generation—the first to hit their targets in vivo with room for improvement as potential treatments. “In terms of therapeutics, this is really the first step,” he said.

In the new study, the team identified and tested a pair of potent synthetic compounds that activate proteins called REV-ERB $\alpha$  and REV-ERB $\beta$ , which play an integral role in regulating

the expression of core clock proteins that drive biological rhythms in activity and metabolism.

In the study, the scientists observed clear metabolic effects when the synthetic compounds were administered twice a day for 12 days. Animals displayed weight loss due to decreased fat mass with no changes in the amount of food they ate. The animals followed the human model of obesity closely, eating a standard Western diet of high fat, high sugar foods, yet still lost weight when given the compounds.

In one of the study's more striking findings, both synthetic compounds were shown to reduce cholesterol production. Cholesterol in the blood of treated animal models decreased 47 percent; triglycerides in the blood decreased 12 percent.

The circadian pattern of expression of a number of metabolic genes in the liver, skeletal muscle, and in fat tissue was also altered, resulting in increased energy expenditure, something of a surprise. In the study, the scientists observed a five percent increase in oxygen consumption, suggesting increased energy expenditure during the day and at night. However, these increases were not due to increased activity—the animals displayed an overall 15 percent decrease in movement during those same time periods.

In addition to its impact on metabolism, the two compounds also affected the animals' activity during periods of light and darkness, suggesting that this class of compound may be useful for the treatment of sleep disorders, including the common problem of jet lag.

The first authors of the study, "Regulation of Circadian Behavior and Metabolism by Synthetic REV-ERB Agonists," are Laura A. Solt and Yongjun Wang of Scripps Research. Other authors include Subhashis Banerjee, Travis Hughes, Douglas J. Kojetin, Thomas Lundasen, Youseung Shin, Jin Liu, Michael D. Cameron, Romain Noel, Andrew A. Butler, and Theodore M. Kamenecka of Scripps Research; and Seung-Hee Yoo and Joseph S. Takahashi of the Howard Hughes Medical Institute and University of Texas Southwestern Medical Center.

The study was supported by the National Institutes of Health and the Howard Hughes Medical Institute.

## **Scripps Florida Scientists Shed Light on Age-Related Memory Loss and Possible Treatments**

### *Fruit Flies Offer Insights on Aging*

Scientists from the Florida campus of The Scripps Research Institute have shown in animal models that the loss of memory that comes with aging is not necessarily a permanent thing.

In a new study published this week in an advance, online edition of the journal *Proceedings of the National Academy of Science*, Ron Davis, chair of the Department of Neuroscience at Scripps Florida, and Ayako Tonoki-Yamaguchi, a research associate in Davis's lab, took a close look at memory and memory traces in the brains of both young and old fruit flies.

What they found is that like other organisms—from mice to humans—there is a defect that occurs in memory with aging. In the case of the fruit fly, the ability to form memories lasting a few hours (intermediate-term memory) is lost due to age-related impairment of the function of certain neurons. Intriguingly, the scientists found that stimulating those same neurons can reverse these age-related memory defects.

“This study shows that once the appropriate neurons are identified in people, in principle at least, one could potentially develop drugs to hit those neurons and rescue those memories affected by the aging process,” Davis said. “In addition, the biochemistry underlying memory formation in fruit flies is remarkably conserved with that in humans so that everything we learn about memory formation in flies is likely applicable to human memory and the disorders of human memory.”

While no one really understands what is altered in the brain during the aging process, in the current study the scientists were able to use functional cellular imaging to monitor the changes in the fly's neuron activity before and after learning.

“We are able to peer down into the fly brain and see changes in the brain,” Davis said. “We found changes that appear to reflect how intermediate-term memory is encoded in these neurons.”

Olfactory memory, which was used by the scientists, is the most widely studied form of memory in fruit flies—basically pairing an odor with a mild electric shock. These tactics produce short-term memories that persist for around a half-hour, intermediate-term memory that lasts a few hours, and long-term memory that persists for days.

The team found that in aged animals, the signs of encoded memory were absent after a few hours. In that way, the scientists also learned exactly which neurons in the fly are altered by aging to produce intermediate-term memory impairment. This advance, Davis notes, should greatly help scientists understand how aging alters neuronal function.

Intriguingly, the scientists took the work a step further and stimulated these neurons to see if the memory could be rescued. To do this, the scientists placed either cold-activated or heat-activated ion channels in the neurons known to become defective with aging and then used cold or heat to stimulate them. In both cases, the intermediate-term memory was successfully rescued.

The study, “Aging Impairs Intermediate-Term Behavioral Memory by Disrupting the Neuron Memory Trace,” was supported by the Ellison Medical Foundation and the Japan Society for the Promotion of Science.

## **Scripps Florida Scientists Identify Neurotransmitters that Lead to Forgetting**

While we often think of memory as a way of preserving the essential idea of who we are, little thought is given to the importance of forgetting to our wellbeing, whether what we forget belongs in the “horrible memories department” or just reflects the minutia of day-to-day living.

Despite the fact that forgetting is normal, exactly how we forget—the molecular, cellular, and brain circuit mechanisms underlying the process—is poorly understood.

Now, in a study that appears in the May 10, 2012 issue of the journal *Neuron*, scientists from the Florida campus of The Scripps Research Institute have pinpointed a mechanism that is essential for forming memories in the first place and, as it turns out, is equally essential for eliminating them after memories have formed.

“This study focuses on the molecular biology of active forgetting,” said Ron Davis, chair of the Scripps Research Department of Neuroscience who led the project. “Until now, the basic thought has been that forgetting is mostly a passive process. Our findings make clear that forgetting is an active process that is probably regulated.”

### *The Two Faces of Dopamine*

To better understand the mechanisms for forgetting, Davis and his colleagues studied *Drosophila* or fruit flies, a key model for studying memory that has been found to be highly applicable to humans. The flies were put in situations where they learned that certain smells were associated with either a positive reinforcement like food or a negative one, such as a mild electric shock. The scientists then observed changes in the flies’ brains as they remembered or forgot the new information.

The results showed that a small subset of dopamine neurons actively regulate the acquisition of memories and the forgetting of these memories after learning, using a pair of dopamine receptors in the brain. Dopamine is a neurotransmitter that plays an important role in a number of processes including punishment and reward, memory, learning and cognition.

But how can a single neurotransmitter, dopamine, have two seemingly opposite roles in both forming and eliminating memories? And how can these two dopamine receptors serve acquiring memory on the one hand, and forgetting on the other?

The study suggests that when a new memory is first formed, there also exists an active, dopamine-based forgetting mechanism—ongoing dopamine neuron activity—that begins to erase those memories unless some importance is attached to them, a process known as consolidation that may shield important memories from the dopamine-driven forgetting process.

The study shows that specific neurons in the brain release dopamine to two different receptors known as dDA1 and DAMB, located on what are called mushroom bodies because of their shape; these densely packed networks of neurons are vital for memory and learning in insects. The study found the dDA1 receptor is responsible for memory acquisition, while DAMB is required for forgetting.

When dopamine neurons begin the signaling process, the dDA1 receptor becomes overstimulated and begins to form memories, an essential part of memory acquisition. Once that memory is acquired, however, these same dopamine neurons continue signaling. Except this time, the signal goes through the DAMB receptor, which triggers forgetting of those recently acquired, but not yet consolidated, memories.

Jacob Berry, a graduate student in the Davis lab who led the experimentation, showed that inhibiting the dopamine signaling after learning enhanced the flies' memory. Hyperactivating those same neurons after learning erased memory. And, a mutation in one of the receptors, dDA1, produced flies unable to learn, while a mutation in the other, DAMB, blocked forgetting.

### *Intriguing Issues*

While Davis was surprised by the mechanisms the study uncovered, he was not surprised that forgetting is an active process. "Biology isn't designed to do things in a passive way," he said. "There are active pathways for constructing things, and active ones for degrading things. Why should forgetting be any different?"

The study also brings into a focus a lot of intriguing issues, Davis said—savant syndrome, for example.

"Savants have a high capacity for memory in some specialized areas," he said. "But maybe it isn't memory that gives them this capacity, maybe they have a bad forgetting mechanism. This also might be a strategy for developing drugs to promote cognition and memory—what about drugs that inhibit forgetting as cognitive enhancers?"

In addition to Davis and Berry, authors of the paper "Dopamine is required for Learning and Forgetting in *Drosophila*" include Isaac Cervantes-Sandoval and Eric P. Nicholas, also of Scripps Research. See [http://www.cell.com/neuron/abstract/S0896-6273\(12\)00338-8](http://www.cell.com/neuron/abstract/S0896-6273(12)00338-8). The study was supported by the National Institutes of Health.

## **Scripps Florida Scientists Identify New Molecules Important for Vision and Brain Function**

In a pair of related studies, scientists from the Florida campus of The Scripps Research Institute have identified several proteins that help regulate cells' response to light—and

the development of night blindness, a rare disease that abolishes the ability to see in dim light.

In the new studies, published recently in the journals *Proceedings of the National Academy of Sciences (PNAS)* and *The Journal of Cell Biology*, Scripps Florida scientists were able to show that a family of proteins known as Regulator of G protein Signaling (RGS) proteins plays an essential role in vision in a dim-light environment.

“We were looking at the fundamental mechanisms that shape our light sensation,” said Kirill Martemyanov, a Scripps Research associate professor who led the studies. “In the process, we discovered a pair of molecules that are indispensable for our vision and possibly play critical roles in the brain.”

In the *PNAS* study, Martemyanov and his colleagues identified a pair of regulator proteins known as RGS7 and RGS11 that are present specifically in the main relay neurons of the retina called the ON-bipolar cells.

“The ON-bipolar cells provide an essential link between the retinal light detectors—photoreceptors and the neurons that send visual information to the brain,” explained Martemyanov. “Stimulation with light excites these neurons by opening the channel that is normally kept shut by the G proteins in the dark. RGS7 and RGS11 facilitate the G protein inactivation, thus promoting the opening of the channel and allowing the ON-bipolar cells to transmit the light signal. It really takes a combined effort of two RGS proteins to help the light overcome the barrier for propagating the excitation that makes our dim vision possible.”

In the *Journal of Cell Biology* study, Martemyanov and his colleagues unraveled another key aspect of the RGS7/RGS11 regulatory response—they identified a previously unknown pair of orphan G protein-coupled receptors (GPCRs) that interact with these RGS proteins and dictate their biological function.

GPCRs are a large family of more than 700 proteins, which sit in the cell membrane and sense various molecules outside the cell, including odors, hormones, neurotransmitters, and light. After binding these molecules, GPCRs trigger the appropriate response inside the cell. However, for many GPCRs the activating molecules have not yet been identified and these are called “orphan” receptors.

The Martemyanov group has found that two orphan GPCRs—GPR158 and GPR179—recruit RGS proteins and thus help serve as brakes for the conventional GPCR signaling rather than play an active signaling role.

In the case of retinal ON-bipolar cells, GPR179 is required for the correct localization of RGS7 and RGS11. Their mistargeting in animal models lacking GPR179 or human patients with mutations in the GPR179 gene may account for their night blindness, according to the new study. Intriguingly, in the brain GPR158 appears to play a similar role in localizing RGS



proteins, but instead of contributing to vision, it helps RGS proteins regulate the m-opioid receptor, a GPCR that mediates pleasurable and pain-killing effects of opioids.

“We are really in the very beginning of unraveling this new biology and understanding the role of discovered orphan GPR158/179 in regulation of neurotransmitter signaling in the brain and retina,” Martemyanov said. “The hope is that better understanding of these new molecules will lead to the design of better treatments for addictive disorders, pain, and blindness.”

The first author of the May 15, 2012 *PNAS* study, “Regulators of G Protein Signaling RGS7 and RGS11 Determine the Onset of the Light Response in ON Bipolar Neurons” is Yan Cao of The Scripps Research Institute. Other authors include Johan Pahlberg and Alapakkam P. Sampath of the University of Southern California; Ignacio Sarria of The Scripps Research Institute; and Naomi Kamasawa of the Max Planck Florida Institute. See <http://www.pnas.org/content/109/20/7905.long>

The first author of the June 11, 2012 *Journal of Cell Biology* study, “GPR158/179 Regulate G Protein Signaling by Controlling Localization and Activity of the RGS7 Complexes” is Cesare Orlandi of The Scripps Research Institute. Other authors include Ekaterina Posokhova and Ikuo Masuho of The Scripps Research Institute and Thomas A. Ray, Nazarul Hasan, and Ronald G. Gregg of the University of Louisville, Kentucky. See <http://jcb.rupress.org/content/197/6/711.abstract>

Both studies were supported by the National Institutes of Health. The *PNAS* study was also supported by the McKnight Endowment Fund for Neurosciences.

## **Researchers Identify Critical ‘Quality Control’ for Cell Growth**

Scientists from the Florida campus of The Scripps Research Institute have identified a series of intricate biochemical steps that lead to the successful production of proteins, the basic working units of any cell.

The study, which appears in the July 6, 2012 edition of the journal *Cell*, sheds light on the assembly of a structure called the ribosome, a large and complex protein-producing machine inside all living cells. Ribosomes are the targets of many commercially used antibiotics and represent a promising area of research because of the importance of ribosome assembly and function for cell growth. There are well-established links between defects in ribosome assembly and cancer, making this pathway a potential new target for anti-cancer drugs.

“With important cellular machines like ribosomes, it makes sense that some process exists to make sure things work correctly,” said Katrin Karbstein, a Scripps Research associate professor who led the study. “We’ve shown that such a quality control function exists for ribosomal subunits that use the system to do a test run but don’t produce a protein. If the

subunits don't pass, there are mechanisms to discard them.”

### *Protein Production Line*

As part of the protein-production process called “translation,” the ribosome decodes information carried in messenger RNA (mRNA) to produce a protein—a chain of amino acids.

To produce mature, functioning ribosomal RNAs (rRNAs), the body first makes precursor rRNAs that can be processed into mature ones. In human cells, this is done in two stages—the first occurs in the nucleolus, a protein-nucleic acid structure inside the nucleus, and finally in the cytoplasm, the basic cellular stew where protein translation occurs. In the cytoplasm, these pre-mature ribosomal subunits encounter large pools of mature subunits, messenger RNA, and numerous assembly factors and translation factors that help complete the process.

During the final maturation process, various assembly factors prevent the translation process from acting on the subunits prematurely, which would result in their rapid degradation or in the production of incorrectly assembled proteins, both processes with potentially lethal outcomes for the cell.

### *Trial Run*

While the work of these assembly factors explains how premature translation is blocked, their presence raises another important question, Karbstein said—Does the conversion of inactive assembly intermediates into mature ribosomes require checkpoints to assure that subunits are functional?

In the study, Karbstein and her colleagues were able to show that during this translation-like cycle the newly made ribosome subunit initially joins with its complementary preexisting subunit to form a much larger complex through the influence of a single translation factor.

This large ribosome complex contains no messenger RNA, which is blocked by assembly factors, and thus produces no protein. Once the major functions of the smaller ribosome subunit have been inspected and approved, another translation factor breaks up the complex and actual protein production occurs.

“What is important here is that the test cycle involves the same translational factors that are involved in normal translation,” Karbstein said. “It’s the most elegant and efficient way to produce perfect ribosomes.”

Interestingly, the study noted, the majority of assembly factors involved in this translation-like test cycle are conserved in creatures ranging from one-celled organisms to humans, suggesting that this evolutionary mechanism is common to all.

The first author of the study, “Joining of 60S Subunits and a Translation-like Cycle in 40S Ribosome Maturation” is Bethany S. Strunk of Scripps Research. Other authors include Megan N. Novak, an undergraduate from Furman University who worked at Scripps as a summer intern, and Crystal L. Young, also of Scripps Research. See <http://www.sciencedirect.com/science/article/pii/S0092867412006459>  
The study was supported by the National Institutes of Health, the National Science Foundation, and the Scripps Research Kellogg School of Science and Technology.

## **Scientists Show Positive Memories Linger Longer**

If you believe positive reinforcement works better than the negative kind, a new study by scientists from the Florida campus of The Scripps Research Institute backs up your beliefs—at least in regard to fruit fly memory formation.

In a new study published in the July 10, 2012 print edition of the journal *Current Biology*, Scripps Florida scientists were able to show that when it comes to learning and memory in the common fruit fly (*Drosophila*), positive reinforcement—in this case, sucrose—results in the formation of a memory trace that lasts twice as long as aversive or negative reinforcement.

Even more remarkable, the flies in the study were able to distinguish between non-nutritive sugars and sucrose, which offers both sweetness and nutrient value—in other words, seemingly unlike most humans, the flies were able to distinguish between good calories and empty ones and hold it in their memory.

The memories formed in flies that were given the non-nutritive sugar decayed within 24-hours—similar, in fact, to those that received the negative reinforcement.

“One of the intriguing things we learned in this study is that there is a molecular nutrient sensor telling the fly that sucrose is good for them,” said Ron Davis, Scripps Research professor and chairman of the Department of Neuroscience, who co-authored the study with Isaac Cervantes-Sandoval, a research associate in his lab. “When this sensor says this is a nutrient capable of supporting life, that information somehow enters the memory circuits and makes it stick.”

The persistence of this nutrient memory is impressive, Davis pointed out. While the memory of a single training trial with negative conditioning decays over one day, a single trial using positive nutritious conditioning forms a stable, long-term memory, lasting as long as four days.

There is also a molecular fingerprint in the brain that distinguishes the memories formed from this nutritious reinforcement. “We can see and measure this fingerprint using sophisticated imaging techniques and have located the memory to what are known as the dorsal paired medial neurons or DPM neurons,” Davis said. After being fed the nutritious

sucrose, the fingerprint for memories of nutrient sugars are found on both of two branches of the DPM neurons, while the fingerprint for memories of non-nutrient or negative reinforcement is confined to only one.

The fingerprint for nutrient memories lasts twice as long as the others, so “it’s both a qualitative and a quantitative difference between the positive and negative memory traces, which is significant,” Davis said.

Davis now wants to know about the sensor that tells the flies what’s good for them and what isn’t. “What is the sensor and where is it located? How does that information enter into the circuitry of learning and memory? That’s where we want to go next,” he said.

The study, “Distinct Traces for Appetitive versus Aversive Olfactory Memories in DPM Neurons of *Drosophila*,” was funded by the National Institutes of Health. See [http://www.cell.com/current-biology/abstract/S0960-9822\(12\)00530-1?switch=standard](http://www.cell.com/current-biology/abstract/S0960-9822(12)00530-1?switch=standard)

## **Scientists Identify a Critical Tumor Suppressor for Cancer**

Scientists from the Florida campus of The Scripps Research Institute have identified a protein that impairs the development and maintenance of lymphoma (cancer of the lymph nodes), but is repressed during the initial stages of the disease, allowing for rapid tumor growth.

While the study, published in the August 3, 2012 edition of the journal *Cell*, largely focuses on the role of this new tumor suppressor in lymphoma induced by Myc oncoproteins (the cancer-promoting products of Myc oncogenes), the authors show this circuit is apparently operational in all human tumors with MYC involvement, which is more than half of all human tumor types.

“This opens a new therapeutic avenue to exploit for cancers with Myc involvement—including relapsed metastatic tumors and refractory tumors, those that have not responded to treatment,” said John Cleveland, a Scripps Research professor and chair of the Department of Cancer Biology, who led the study.

The Myc family of oncoproteins (c-Myc, N-Myc, and L-Myc) regulate critical pathways that contribute to tumors; c-Myc expression, which is activated in human Burkitt lymphoma, is sufficient to induce the growth of several tumor types in animal models.

In the new study, the scientists focused on precancerous and malignant Myc-expressing B cells, part of the immune system affected in human lymphoma. Using transgenic animal models, Cleveland and his team, led by the efforts of senior postdoctoral fellow Robert Rounbehler, showed that Myc-directed repression of a protein called tristetraprolin (TTP/ZFP36) was important for both the development and maintenance of cancer. The

suppression of TTP is a hallmark of human cancers with MYC involvement, Cleveland noted.

The scientists' results showed that overriding this pathway by forced expression of TTP more than doubled the lifespan of Myc transgenic mice. Strikingly, Rounbehler discovered that re-introduction of TTP into Myc-driven lymphoma totally disabled these tumors, indicating an important therapeutic target.

The authors showed that Myc regulates hundreds of genes that contain adenylate-uridylate-rich elements (AU-rich elements), which play an important role in RNA stability and are found in many messenger RNAs (mRNAs) that code for oncogenes, nuclear transcription factors, and cytokines. AU-rich elements direct the mRNA for degradation; they are thought to be vital for controlling expression during cell growth.

"Myc regulates the expression of select AU-binding proteins to control the destruction of certain mRNAs," Cleveland said. "Also, our study strongly suggests that other AU-binding proteins may also, in fact, function as tumor suppressors in other cancers."

The first author of the study, "Tristetraprolin is a Tumor Suppressor That Impairs Myc-Induced Lymphoma and Abolishes the Malignant State," is Robert J. Rounbehler of Scripps Research. Other authors include Mohammad Fallahi, Chunying Yang, Meredith A. Steeves, Weimin Li, Joanne R. Doherty, and Franz X. Schaub of Scripps Research; Sandhya Sanduja and Dan A. Dixon of the University of South Carolina; and Perry J. Blackshear of the National Institute of Environmental Health Sciences. See [http://www.cell.com/abstract/S0092-8674\(12\)00766-0](http://www.cell.com/abstract/S0092-8674(12)00766-0)

The study was supported by the National Institutes of Health (grant numbers DK44158, CA167093, F32-CA115075, and CA134609), ThinkPink Kids Foundation, the State of Florida, the National City Charitable Contributions Committee, the Glenn W. Bailey Postdoctoral Fellowship, and the PGA National Women's Cancer Awareness Days.

### **Team Shows Potent New Compound Virtually Eliminates HIV in Cell Culture**

A new study by scientists on the Florida campus of The Scripps Research Institute shows, in cell culture, a natural compound can virtually eliminate human immunodeficiency virus (HIV) in infected cells. The compound defines a novel class of HIV anti-viral drugs endowed with the capacity to repress viral replication in acutely and chronically infected cells.

The HIV/AIDS pandemic continues to affect 34 million individuals worldwide, including more than 3 million children, according to the World Health Organization. Current treatment involves the use of several antiretroviral drugs, termed Highly Active Antiretroviral Therapy (HAART), which can extend the life expectancy of HIV-positive individuals and decrease viral load without, however, eradicating the virus.

“We know that there are reservoirs of HIV that aren’t being eliminated by current treatment and that keep replenishing the infection,” said Susana Valente, a Scripps Research biologist who led the study. “Viral production from these cellular reservoirs that harbor an integrated viral genome is not affected by current antiretroviral drugs, which only stop novel rounds of infection. The compound in the current study virtually eliminates all viral replication from already-infected cells where HIV hides.”

The new study, published in the July 20, 2012 issue of the journal *Cell Host and Microbe*, focused on a medically promising compound known as Cortistatin A. This natural product was isolated in 2006 from a marine sponge, *Corticium simplex*, discovered more than 100 years ago. In 2008, Scripps Research chemist Phil Baran and his team won the global race to synthesize the compound, presenting an efficient and economical method.

In the new study, Valente and her colleagues collaborated with the Baran lab, using a synthetic version of the compound, didehydro-Cortistatin A, to study the compound’s effect on two strains of HIV. The strains were HIV-1, the most common form of the virus, and HIV-2, which is concentrated in West Africa and some parts of Europe.

The results showed that the compound reduced viral production by 99.7 percent from primary CD4+T cells (a type of immune cell) isolated from patients without levels of the virus in their bloodstream and who had been under HAART treatment for a long period of time. When the compound was added to other antiviral treatments, it further reduced by 20 percent viral replication from CD4+T cells isolated from patients with detectable amounts of virus in their bloodstreams.

The inhibitor works by binding tightly to the viral protein known as Tat, a potent activator of HIV gene expression, effectively preventing the virus from replicating even at miniscule concentrations—making it the most potent anti-Tat inhibitor described to date, Valente said.

Another interesting feature of this compound is that withdrawal of the drug from cell culture does not result in virus rebound, which is normally observed with other antiretrovirals.

While most antiretroviral compounds block only new infections, didehydro-Cortistatin A reduces viral replication from already-infected cells, potentially limiting cell-to-cell transmission.

The new inhibitor already has a drug-like structure, is effective at very low concentrations, and has no toxicity associated with it, at least at the cellular level, the study noted. The first author of the study “Potent Suppression of Tat-dependent HIV Transcription by didehydro-Cortistatin A” is Guillaume Mousseau of Scripps Research. In addition to Valente and Baran, other authors include Mark A. Clementz, Wendy N. Bakeman, Nisha Nagarsheth, Michael Cameron, and Jun Shi of Scripps Research; and Rémi Fromentin and Nicolas Chomont of the Vaccine and Gene Therapy Institute. See [http://www.cell.com/cell-host-microbe/abstract/S1931-3128\(12\)00202-8](http://www.cell.com/cell-host-microbe/abstract/S1931-3128(12)00202-8)

The study was supported by the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) and the Landenberger Foundation.

### **Scientists Design Molecule that Reverses Some Fragile X Syndrome Defects**

Scientists on the Florida campus of The Scripps Research Institute have designed a compound that shows promise as a potential therapy for one of the diseases closely linked to fragile X syndrome, a genetic condition that causes mental retardation, infertility, and memory impairment, and is the only known single-gene cause of autism.

The study, published online ahead of print in the journal *ACS Chemical Biology* September 4, 2012, focuses on tremor ataxia syndrome, which usually affects men over the age of 50 and results in Parkinson's like-symptoms—trembling, balance problems, muscle rigidity, as well as some neurological difficulties, including short-term memory loss and severe mood swings.

With fragile X syndrome, tremor ataxia syndrome, and related diseases, the root of the problem is a structural motif known as an “expanded triplet repeat”—in which a series of three nucleotides are repeated more times than normal in the genetic code of affected individuals. This defect, located in the fragile X mental retardation 1 (FMR1) gene, causes serious problems with the processing of RNA.

“While there is an abundance of potential RNA drug targets in disease, no one has any idea how to identify or design small molecules to target these RNAs,” said Mathew Disney, a Scripps Research associate professor who led the study. “We have designed a compound capable of targeting the right RNA and reversing the defects that cause fragile X-associated tremor ataxia.”

#### *Preventing Havoc*

In tremor ataxia syndrome, the expanded triplet repeat leads to the expression of aberrant proteins that wreak widespread havoc. The repeats actually force the normal proteins that regulate RNA splicing—necessary for production of the right kind of proteins—into hiding. The compound designed by Disney and his colleagues not only improves the RNA splicing process, but also minimizes the ability of repeats to wreak havoc on a cell.

“It stops the repeat-associated defects in cell culture,” Disney said, “and at fairly high concentrations, it completely reverses the defects. More importantly, the compound is non-toxic to the cells. It looks like a very good candidate for development, but we’re still in the early stages of testing.”

Overall, this study reinforces Disney's earlier findings showing it is possible to identify and develop small molecules that target these traditionally recalcitrant RNA defects. In March

of this year, Disney published a study in the Journal of the American Chemical Society (<http://www.ncbi.nlm.nih.gov/pubmed/22300544>) that described a small molecule that inhibited defects in myotonic dystrophy type 1 RNA in both cellular and animal models of disease.

“We’ve gotten very good at targeting RNA with small molecules, something a lot of people said couldn’t be done,” Disney pointed out. “Our approach is evolving into a general method that can be used to target any disease that is associated with an RNA, including, perhaps, fragile X syndrome itself.”

The new compound also works as a probe to better understand how these repeats cause fragile X syndrome and how they contribute to tremor ataxia, Disney added.

In addition to Disney, authors of the study, “Small Molecule That Targets r(CGG) and Improves Defects in 2 Fragile X Associated Tremor Ataxia Syndrome,” include Biao Liu, Wang-Yong Yang, Tuan Tran, and Jessica L. Childs-Disney of Scripps Research; and Nicolas Charlet-Berguerand and Chantal Sellier of the Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Institut National de la Santé et de la Recherche Médicale (INSERM), the Centre National de la Recherche Scientifique (CNRS), and University of Strasbourg, Illkirch, France. For more information on the paper, see <http://pubs.acs.org/doi/full/10.1021/cb300135h>

The study was funded by the National Institutes of Health (award numbers 3R01GM079235-02S1 and 1R01GM079235-01A2), INSERM, the French National Research Agency, and The Scripps Research Institute.

### **Study Uncovers Link Between Hormone Levels and Risk for Metabolic Disease**

Working with a national team of researchers, a scientist from the Florida campus of The Scripps Research Institute has shown for the first time a link between low levels of a specific hormone and increased risk of metabolic disease in humans.

The study, published online ahead of print in *The Journal of Clinical Endocrinology & Metabolism*, focuses on the hormone adropin, which was previously identified by Associate Professor Andrew Butler’s laboratory during an investigation of obese and insulin-resistant mice. Adropin is believed to play an important role in regulating glucose levels and fatty acid metabolism.

“The results of this clinical study suggest that low levels of adropin may be a factor increasing risk for developing metabolic disorders associated with obesity and insulin resistance, which could then lead to diseases such as type 2 diabetes,” said Butler, who led the new study with Peter J. Havel, professor of molecular biosciences and nutrition at the University of California, Davis.



Approximately 47 million adults in the United States have metabolic syndrome, according to the American College of Cardiology. The National Institutes of Health defines metabolic syndrome as a group of risk factors, especially obesity and insulin resistance, that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes.

### *Intriguing Results*

In the new study, which involved 85 women and 45 men, Butler and his colleagues showed that obesity is associated with lower adropin levels. Lower adropin levels were also observed in individuals with a higher “metabolic syndrome risk factor” score, a score determined by measuring triglycerides, LDL cholesterol, HDL, glucose, blood pressure, and waist circumference.

The scientists also observed circulating adropin concentrations increased significantly at three and six months following gastric bypass surgery in morbidly obese patients. Interestingly, adropin levels returned to pre-surgical levels at 12 months after surgery.

Another surprising finding of the new study was that in people of normal weight, women had lower plasma adropin levels than men. In addition, obesity had a bigger negative effect on adropin levels in men. Interestingly, obesity in woman was also not associated with lower plasma adropin levels. The significance of the differences between men and woman is unknown at the moment.

“But the link between low levels of adropin and increased metabolic risk was observed in both sexes,” Butler said. “The impact is there, irrespective of gender.”

Adropin levels were also found in general to decrease with age—the decline was highest in those over 30 years of age. As with obesity, the aging effect appeared to be more pronounced in men.

### *Findings in Humans Mirror Preclinical Work*

The new study is an important extension of earlier pre-clinical studies using animal models published in the July edition of *Obesity* (<http://www.nature.com/oby/journal/v20/n7/full/oby201231a.html>). In that study, Butler and colleagues deleted the gene encoding adropin from mice. The scientists found that, while normal in appearance, adropin-deficient mice have insulin resistance and, when fed diets with a high fat content, develop a more severe impaired glucose tolerance (IGT). These findings suggest reduced insulin production and attenuated response to insulin, which are the defining features of type 2 diabetes. Importantly, mice having only one functional copy of the gene encoding adropin also exhibited increased propensity for developing impaired glucose tolerance with obesity. These findings provided important pre-clinical evidence that low levels of adropin are associated with increased risk of developing type 2 diabetes.

In other studies, Butler's laboratory observed that obese mice exhibit dramatic reductions in circulating adropin levels, and that insulin resistance was reversed after injections with a synthetic form of adropin.

"The data from these studies provide strong evidence suggesting that low levels of adropin may be an indicator of risk for insulin resistance in obesity and, consequently, an increased risk for metabolic diseases, including type 2 diabetes," Butler said. "We see a lot of similarity between animal model data and the new human data—low adropin levels in humans are associated with a host of metabolic syndrome risk factors normally associated with obesity and insulin resistance."

Taken together, these studies suggest the possibility that therapeutics designed to boost the supply of adropin might be useful in fighting obesity and metabolic disease.

In addition to Butler and Havel, authors of the study, "Low Circulating Adropin Concentrations With Obesity And Aging Correlate With Risk Factors For Metabolic Disease And Increase After Gastric Bypass Surgery In Humans," include Charmaine S. Tam and Eric Ravussin of Louisiana State University, Baton Rouge; Kimber L. Stanhope and Mohamed R. Ali of the University of California, Davis; Bruce M. Wolfe of the Oregon Health Sciences University, Portland; and Majella O'Keeffe and Marie-Pierre St Onge of Columbia University. For more information on the study, see <http://jcem.endojournals.org/content/early/2012/08/07/jc.2012-2194.abstract>.

The study was supported by the National Institutes of Health (award numbers HL061352, DK060412, HL075675, HL09133, UL1 RR024156-03, UL1 RR024146, and 1P30 DK072476-06); the American Diabetes Association; The Novo Nordisk Diabetes Innovation Award Program; the University of California, Davis Health Care Systems Award; the Irving Center for Translational Science; and the Pennington Biomedical Research Center's Nutrition Obesity Research Center program.