SCRIPPS DISCOVERS

Accelerating Discoveries, Saving Lives

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RESEARCH UPDATE

Scripps Florida Scientists Design a Potential Drug Compound that Attacks Parkinson's Disease on Two Fronts

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have found a compound that could counter Parkinson's disease in two ways at once.

In a new study published recently by the journal *ACS Chemical Biology*, the scientists describe a "dual inhibitor"—two compounds in a single molecule—that attacks a pair of proteins closely associated with development of Parkinson's disease.

"In general, these two enzymes amplify the effect of each other," said team leader Phil LoGrasso, a TSRI professor who has been a pioneer in the development of JNK inhibitors for the treatment of neurodegenerative diseases. "What we were looking for is a high-affinity, high-selectivity treatment that is additive or synergistic in its effect—a one-two punch."

Now the team's new dual inhibitor will need to be optimized for potency, high selectivity (which reduces off-target side effects) and bioavailability so it can be tested in animal models of Parkinson's disease.

Professor Phil LoGrasso

Scripps Research Institute Scientists Find 3D Structure of Key Drug Target for Diabetes

Professor Raymond Stevens

An international team led by scientists at The Scripps Research Institute (TSRI) has determined and analyzed the three-dimensional atomic structure of the human glucagon receptor. The receptor, found mainly on liver and kidney cells, helps regulate glucose levels in the bloodstream and is the target of potential therapeutic agents for type 2 diabetes.

"Our data should change the current view of how drugs are designed with this and related receptors," said TSRI Research Associate Fai Yiu Siu, PhD, who was first author of the study.

The study was reported in the journal *Nature*, alongside a British laboratory's structural study of another member of the same class of receptors—known as "class B" G protein-coupled receptors (GPCRs).

"Understanding how the glucagon receptor interacts with and binds to its partners will provide new information on how cells maintain sugar levels, possibly aiding the development of

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Inside:

Scripps Florida Scientists Turn Muscular Dystrophy Defect On and Off in Cells

Associate Professor Matthew Disney

For the first time, scientists from the Florida campus of The Scripps Research Institute (TSRI) have identified small molecules that allow for complete control over a genetic defect responsible for the most common adult onset form of muscular dystrophy. These small molecules will enable scientists to investigate potential new therapies and to study the long-term impact of the disease.

"This is the first example I know of at all where someone can literally turn on and off a disease," said TSRI Associate Professor Matthew Disney, whose new research was published June 28, 2013, by the journal *Nature Communications*. "This easy approach is an entirely new way to turn a genetic defect off or on."

Myotonic dystrophy is an inherited disorder, the most common form of a group of conditions called muscular dystrophies that involve progressive muscle wasting and weakness. Myotonic dystrophy type 1 is caused by 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, a cytosine-uracil-guanine (CUG) triplet repeat binds to the protein MBNL1, rendering it inactive and resulting in RNA splicing abnormalities.

To find drug candidates that act against the defect, Disney and his colleagues analyzed the results of a National Institutes of Health (NIH)-sponsored screen of more than 300,000 small molecules that inhibit a critical RNA-protein complex in the disease.

Preclinical Study Shows Heroin Vaccine Blocks Relapse

Scientists at The Scripps Research Institute (TSRI) have reported successful preclinical tests of a new vaccine against heroin. The vaccine targets heroin and its psychoactive breakdown products in the bloodstream, preventing them from reaching the brain.

"Heroin-addicted rats deprived of the drug will normally resume using it compulsively if they regain access, but our vaccine stops this from happening," said George F. Koob, who chairs TSRI's addiction research group, the Committee on the Neurobiology of Addictive Disorders. If the vaccine works as well in human trials, it could become a standard part of therapy for heroin addiction, which is estimated to affect more than 10 million people worldwide.

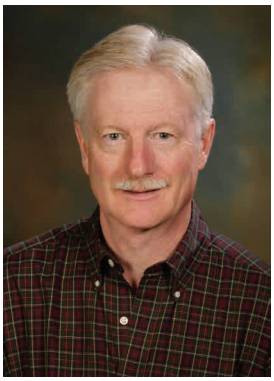
Koob, TSRI Professor Kim Janda, and their laboratories led the study, which appeared in the *Proceedings of the National Academy of Sciences*.

The heroin vaccine is one of several vaccines against drugs of abuse that have been developed since the 1990s by scientists at TSRI and other institutions.

The structures of common drug molecules are too small and simple to stimulate the immune system sufficiently on their own, but vaccine designers have overcome this hurdle by affixing key fragments of drug molecules to larger, more immune-provoking carrier proteins. Vaccines against cocaine and nicotine that have been designed this way are now in clinical testing, and a methamphetamine vaccine is nearing readiness for such tests.

Designing an effective vaccine against heroin has been particularly challenging because the drug breaks down rapidly in the bloodstream after injection. "Heroin is metabolized very quickly to another compound called 6-acetylmorphine, which crosses into the brain and accounts for much of heroin's effect," said Janda, who is TSRI's Ely R. Callaway, Jr. Chair in Chemistry and whose laboratory initially developed the vaccine three years ago.

Janda and his team therefore designed the heroin vaccine to elicit antibodies against not only heroin, but also 6-acetylmorphine and morphine. "The vaccine effectively tracks the drug as it is metabolized, keeping the active breakdown products out of the brain, and that, I think, explains its success," Janda said.



Professor George Koob

Professor Kim Janda

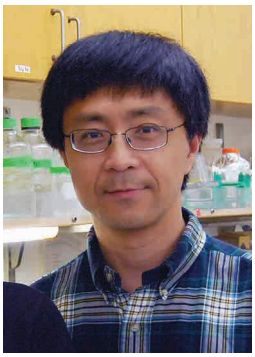
Scripps Research Institute Scientists Uncover New Details of Natural Anticancer Mechanism

Scientists at The Scripps Research Institute (TSRI) have identified key triggers of an important cancer-blocking mechanism in cells.

Termed "oncogene-induced senescence," this mechanism can block most cancer types, and is commonly experienced when incipient skin cancers turn instead into slow-growing moles. Tumors that achieve malignancy often do so by defeating or circumventing this growth barrier—which is why scientists have been eager to find out precisely how it works.

"We have known about some of the molecular signals that mediate this senescence response, but we've needed to understand the signaling pathway in much more detail," said Peiqing Sun, associate professor in TSRI's Department of Cell and Molecular Biology.

In the new study, published recently by the journal *Molecular Cell*, Sun and his colleagues describe the cascading interactions of three enzymes that are necessary to initiate a common type of oncogene-induced senescence.



Associate Professor Peiqing Sun

It's Never too Early to Start Planning for Your Year-End Giving

> December 31, 2013 will be here before you know it! It's time to start planning for your year-end gifts to support The Scripps Research Institute. Here are some helpful ways to give to start your planning.

Cash – The simplest way to make a gift to The Scripps Research Institute (TSRI) is to write a check or use your credit card. When itemizing your deductions, gifts of cash can be deducted up to 50 percent of your adjusted gross income; any excess can be deducted over the next five years.

Securities or Mutual Funds – Transfer appreciated assets (stocks, bonds) held for more than one year to us and enjoy an income tax charitable deduction for the full market value. No capital gains tax is due on the appreciated value.

Life Income Gifts – There are a variety of gifts that can provide an income to you. A Charitable Gift Annuity is one of the more popular life income gifts. Simply donate cash or securities in exchange for fixed annuity payments. Enjoy a current income tax deduction for the gift and tax-free return of principal. Also, when the donor is the annuitant, any capital gains tax due is spread over the donor's lifetime. You may designate your future gift from a charitable gift annuity per your interest and wishes. Still other examples of life income gifts are available. Simply contact us for more information or a confidential gift illustration or visit our website at www.plannedgiving.scripps.edu.

IRA Charitable Rollover – If you are 70½, have an Individual Retirement Account and must take a required minimum distribution (RMD), you may wish to take advantage of transferring (rolling) your annual contribution to The Scripps Research Institute. It is easy to do — just tell the IRA administrator to send us your gift (any amount up to $100,000), and let us know to expect it. Hurry, as this popular way to give expires on December 31, 2013.

Retirement Plan Assets – Add The Scripps Research Institute, as a beneficiary designation to your qualified retirement plan. TSRI's Tax ID Number is 33-0435954. You can use a retirement plan to realize philanthropic goals and avoid income tax on plan assets (income in respect of a decedent).

We look forward to helping you maximize your charitable and financial goals. For more information about your giving options, please contact Geoff Graham at (858) 784-9365 or gcgraham@scripps.edu.

When considering charitable gifts you are urged to seek the advice of your own financial and legal advisor(s) about your specific situation.

60 Seconds with: TSRI Professor Hugh Rosen

What are your goals?

I've dedicated my career to finding unique biological pathways that govern disease and to discover drugs that can influence those pathways.

What would you call your greatest successes?

A major contribution was showing how vital cellular structures called $S1P_1$ receptors control the flow of lymphocytes, a type of white blood cell, out of and then back into lymph nodes. These receptors have clear medical importance. In multiple sclerosis, the lymphocytes attack the protective sheaths around nerve cells in the central nervous system, sparking nerve misfires and scarring, and leading to pain and debilitation in MS sufferers. Modulation of $S1P_1$ is clinically useful in treating the disease.

This work in the Rosen and Ed Roberts laboratories, began with a screen performed in the National Institutes of Health-funded Molecular Screening Center at TSRI and led to a novel, selective S1P1 receptor agonist called RPC-1063, now licensed to the company Receptos. It has now entered Phase II/III clinical trials for MS and ulcerative colitis, an inflammatory bowel disease.

It's a huge breakthrough any time you discover something that impacts patients. If you save a single life, you save an entire world.

The impact of our discovery efforts is not limited to MS. Ed Roberts and I are also studying a receptor that binds with naturally occurring compounds similar to drugs such as opium. This receptor's activity plays critical roles in controlling anxiety and depression. We've identified promising compounds that may regulate this activity as a potential treatment for post-traumatic stress disorder. We've also discovered a vasopressin 1A receptor antagonist for symptoms and the treatment of autism spectrum disorders, and we are working together with TSRI to define the best path forward for these new molecules to impact on the lives and dignity of patients.

Professor Hugh Rosen

Why did you come to TSRI and what do you like about working here?

I came to TSRI from Merck in 2002 because it is a special and attractive place to make discoveries. At TSRI, I found an environment where clarity of vision was enabled by the cross-disciplinary contributions and excellent colleagues. I cannot stress enough how much I enjoy the scientific collaboration and meeting of minds. And nothing happens except for the hard work and efforts of my colleagues in the lab. Synergy from scientific environment, colleagues, and facilities means our impact on human health can be disproportionately high. At TSRI, we push the boundaries of the scientific and medical fields in exploring better therapeutic possibilities.

Do you need philanthropy in your work?

We always need and welcome partners in this voyage of discovery that brings the best of science and medicine together to improve the health of individuals and populations. It is important for us, and the shared journey of philanthropist and academician to impact on human health is an important contribution and legacy for all parties.

Diabetes, CONTINUED

treatments for glucose-related disorders like type 2 diabetes," said Jean Chin, PhD, of the National Institutes of Health's National Institute of General Medical Sciences, which partially funded the research. "Because the receptor is the first in its class of membrane proteins to be structurally determined, the work may advance studies of similarly shaped, medically important but often difficult to characterize molecules."

TSRI Professor Raymond C. Stevens, PhD, who was a senior author of the study, noted, "This work involved a very fruitful international collaboration in which researchers in the United States, China and Europe worked closely together for more than two years to uncover the key differences in this subfamily of GPCRs."

Eleanor Mosca: Explorer, Caregiver, Educator, Collector… and Supporter of Medical Research!

La Jolla resident Eleanor Mosca is active in a variety of pursuits, and TSRI is thankful that medical research is one of them. A loyal TSRI supporter who frequents our events on recent scientific discoveries, Eleanor has been giving to TSRI since 1985. She is a great advocate of our work and is a member of the Scripps Legacy Society by virtue of her decision to support science at TSRI in her estate plan.

Eleanor's background includes positions as a registered nurse in Boston and Greensboro, North Carolina; a university educator in both nursing and sociology; and a counselor.

She and her husband Carlo moved to La Jolla in 1972 from Boston when Carlo accepted the position of Director of Education at Sea World. Internationally recognized for his work, Carlo had previously been the Director of Education and Graphics at the New England Aquarium and the Director of Exhibit Halls at Boston's Museum of Science.

Carlo passed away tragically at the age of 45 in 1984. He was the eighth patient diagnosed with AIDS in the United States and participated in the Alpha Interferon protocol at Sloan-Kettering. Carlo was the third patient given the drug and initially tested disease free for six months, but then died two months later.

It is now known that treating AIDS with interferon resulted in no benefits to patients and probably accelerated the disease process in some. His illness and death spurred Eleanor's involvement at TSRI. Eleanor realizes that Alpha Interferon has proven effective in many other conditions and is a precise example of why it's important to give to TSRI and medical research.

A major portion of Eleanor's estate is designated to TSRI, with a portion going to Scripps Health, and some to the Friends of Mount Auburn Cemetery in Cambridge Massachusetts. Mount Auburn Cemetery, where Carlo is buried, is not only a cemetery, but a National Historic Landmark, a botanical garden, an outdoor museum of art and architecture, and an important habitat for urban wildlife.

"Medical research is extremely important to me," said Eleanor. "I've always been interested in research of all sorts and started attending lectures at Scripps when Carlo passed away that enhanced my medical knowledge."

"I contribute to research at TSRI because I feel it's the building block for improved health and saving lives," Eleanor continued. "Medical research is often serendipitous – the most significant research usually comes about when people are looking for something else entirely. Many diseases in our lifetime would not have been cured without multi-disciplinary science. What I like about TSRI is that it furthers science by integrating various disciplines like biology, chemistry, physics, and molecular biology."

Eleanor volunteered at the San Diego Humane Society for twelve years. The proud owner of three cats, she is the author of *"The Cat's Tail"*, in honor of her cat "Brick" who passed away in 2010. It's an amusing paperback book on the travails of a stray cat trying to survive before being adopted. Told from the cat's perspective, it's dedicated to the humans who provide food, shelter, care, and companionship for our feline friends. Proceeds from the book went to various cat care organizations around the country.

Her home is a virtual museum – it's filled with various collections, including an array of old-fashioned wooden duck decoys, hand carved shorebirds, tapestries, her own nature photographs, and Intuit art and artifacts. Eleanor lectures about her numerous Arctic explorations (having covered most of the Arctic through her 16 expeditions, some via dog sled). But before her next trip, she is sure to be seen at the next TSRI event!

Eleanor Mosca on one of her numerous Arctic expeditions

Gavin MacBeath: Multi-Disciplinary Training at TSRI Paves Way for Career Developing Cancer Drugs

Gavin MacBeath is a successful alum of The Scripps Research Institute (TSRI), who looks back fondly at his days on the La Jolla, California campus. After receiving his Bachelor's of Science in Genetics from the University of Manitoba in 1991, Gavin became a member of TSRI's second full graduating Ph.D. class in 1997.

"The graduate program was very new at the time," said Gavin. "It was small and one of the few multidisciplinary programs in the country at the interface of chemistry and biology. I had a wonderful time at TSRI. In retrospect, it was one of the best times of my life – I was exposed to so many different areas of study and appreciated how interactive and free-flowing the labs were."

After completing his doctoral work at TSRI with Professor Donald Hilvert (now at the Federal Institute of Technology (ETH) Zurich), Gavin joined the faculty at Harvard University, where he put his training to use unraveling complex biological systems in a search for new drugs. He pioneered the development and use of protein microarray technology which has shed light on how proteins interconnect and how defects in these networks lead to human diseases, such as cancer.

In 2000, Gavin co-founded Merrimack Pharmaceuticals in Cambridge, Massachusetts using the protein microarray technology developed in his lab. The firm, where he currently serves as vice president of translational research, develops innovative medicines paired with companion diagnostics for the treatment of serious diseases, especially cancer. The company now has six novel next-generation therapeutic oncology candidates in clinical trials, and is investigating how personalized and predictive medicine based on a patient's underlying tumor biology could enhance treatment. Last year, 12 years after its founding, the firm went public.

"Merrimack provides the resources and environment needed to address what I believe is the biggest challenge in biomedical research for the twenty-first century – the problem of matching patients to therapies," said Gavin.

Gavin MacBeath

"Research and development at Merrimack over the coming years will determine how important Network Biology is in the context of co-developing drugs and companion diagnostics that identify which patients will respond most effectively to which drugs – this is changing the way we discover drugs."

Even with his heavy workload at Merrimack, Gavin continues to direct a research lab and lecture at Harvard Medical School.

Gavin is enjoying his work tremendously and says that his experience at TSRI has been a big help. "I'm learning a lot about the day-to-day challenges and the process of moving drugs forward through the development process, plus I'm very satisfied knowing that ultimately in the not-too-distant future, my scientific work could be used in practical solutions for patients – it's very rewarding. Learning different tools at the interface of chemistry and biology at TSRI made me fluent in the field and helped me select the right tools to apply in my work today."

Katja Lamia Named Kimmel Scholar for Cancer Research

Katja Lamia, assistant professor in the Department of Chemical Physiology at TSRI, has been named a 2013 Kimmel Scholar by the Sidney Kimmel Foundation for Cancer Research. Lamia is one of just 15 award recipients from a national pool of 150 applicants.

The Kimmel Scholar program aims to advance the careers of gifted young scientists involved in cancer research. Recipients must be in the early stages of their research career, demonstrate the greatest promise and innovation in their work and have not progressed far enough to have received major grants from the National Cancer Institute or other funding sources.

Lamia's lab is investigating the molecular basis for the circadian control of metabolism to enable novel therapies to treat metabolic disease. The two-year Kimmel Scholar grant will support her project.

Scripps Florida Scientists Awarded $1.4 Million to Develop New Therapeutic Approaches to Chronic Leukemia

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have been awarded more than $1.4 million from the National Cancer Institute of the National Institutes of Health to create a potential new drug to attack the malignant cells that cause chronic lymphocytic leukemia (CLL), which is the most common leukemia in the Western world.

Christoph Rader, a TSRI associate professor, will be principal investigator of the new three-year study. William Roush, a TSRI professor, associate dean of graduate studies and executive director of medicinal chemistry, will be co-principal investigator.

CLL affects approximately 150,000 patients and causes 4,500 deaths per year in the United States alone. While chemotherapy and radiation are used to treat this slow growing form of leukemia, currently there are no therapeutic options for the disease in which physicians can selectively target the malignant cells yet spare normal cells and tissues.

The scientists plan to use the recently discovered cell surface receptor TOSO, which is overexpressed in leukemia cells, to create a rapid and effective entry point for delivering drugs to these malignant cells while bypassing normal cells as much as possible.

"We want to create carrier-payload combinations to deliver cytotoxic drugs with very specific targeting," Roush said. "Once we have accomplished that, we expect to optimize potency."

In addition, the team plans to use an antibody fragment to add a second target to the treatment—the receptor tyrosine kinase ROR1, which is expressed exclusively on leukemia cells.

"This dual-targeting strategy will lay the foundation for further preclinical and clinical investigations in the treatment of this form of leukemia," said Rader. "We also think that the novel biological and chemical components that come from this study can be easily exploited to develop combinations for diseases beyond CLL."

Professor William Roush

Associate Professor Christoph Rader

Esther B. O'Keeffe Foundation Donates $250,000 to Fund Scripps Florida Neuroscience Training Program

The Esther B. O'Keeffe Charitable Foundation has made a $250,000 donation to The Scripps Research Institute (TSRI) to fund neuroscience training and public outreach on the Florida campus.

"We're deeply grateful for the support of the O'Keeffe Foundation," said TSRI President and CEO Michael A. Marletta. "This gift will help us train the next generation of neuroscientists, as well as support a series of presentations on brain function and dysfunction to raise broad community awareness of Scripps Florida's work to understand and combat brain diseases."

"Thanks to the O'Keeffe Foundation, we look forward to connecting with the public and with local policy makers to showcase both what we do and the people involved in our research," added Ronald L. Davis, chair of the Department of Neuroscience at Scripps Florida who will oversee the new fund. "Our scientists-in-training will also benefit from the foundation's support."

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 spectrum of arts and cultural programs.

"We are delighted to help contribute to the important scientific and educational work taking place at The Scripps Research Institute," said Clare O'Keeffe, executive trustee of the foundation. "The advances being forged by Scripps Florida scientists are tremendously exciting."

The latest gift from the Esther B. O'Keeffe Charitable Foundation follows gifts totaling more than $3 million to Scripps Florida to fund biomedical research and education. In recognition of the foundation's generosity, last May the Founders Room and the adjoining boardroom on the Florida campus were named the Esther B. O'Keeffe Founders Suite.

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.

California Healthcare Institute Representatives Visit TSRI

Representatives from the California Healthcare Institute (CHI), a public policy organization for biomedical research and industry, visited TSRI in July, learning about TSRI's research programs and the importance of government funding. Pictured here, James Voss, a research associate in the Burton lab, chats with CHI's Erica Hiar (left), director of public relations and communications, and Jenny Carey, associate director of federal government relations and programs.

The Scripps Research Institute

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