

SCRIPPS DISCOVERS

Accelerating Discoveries, Saving Lives

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INSTITUTE UPDATE

Moody's Affirms Institute's Aa3 Credit Rating

Moody's Investors Service has affirmed The Scripps Research Institute's Aa3 long-term credit rating. The rating applies to the institute's Series 2000, Series 2005A and taxable Series 2005B bonds issued through the California Infrastructure and Economic Development Bank.

Moody's noted that the rating incorporates a variety of factors, including the institute's "position as a leading national biomedical research organization," financial reserves, essentially balanced annual operating performance, and new leadership. The rating also takes into account pressures related to national trends of declines in federal grant funding, the conclusion of a long-term general funding strategy involving a single pharmaceutical partner, and the institute's lease and pension obligations.

According to the rating agency, "The rating outlook is stable, reflecting no borrowing plans and slowly growing financial resources, with expectations of generally balanced operating performance as Scripps Florida is brought fully online against successful cost management efforts of Scripps La Jolla, bringing in good operating cash flow and debt service coverage."

RESEARCH UPDATE

Researchers Shed Light on Age-Related Memory Loss and Possible Treatments

> 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 study published in April, in 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."

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Professor Ron Davis

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Clinical Trials Start for Stroke Drug Developed by Scripps Research Institute, USC, and ZZ Biotech

Clinical trials recently started for a stroke drug initially created by a team led by scientists at The Scripps Research Institute and the University of Southern California (USC), and further developed by biotech company ZZ Biotech.

The clinical trials are testing the safety in humans of the experimental drug 3K3A-APC, which has been shown in animal models to reduce brain damage and improve motor skills after stroke when given in conjunction with a federally approved clot-busting therapy.

"I am incredibly excited about the potential for translating our science into a therapy that could have a significant impact on society," said Scripps Research Institute Professor John Griffin, who collaborated on the scientific work with Professor Berislav V. Zlokovic, director of the Zilkha Neurogenetic Institute at the Keck School of Medicine of USC. "Stroke and its aftereffects are a huge problem in this country."

Kent Pryor, chief operating officer of ZZ Biotech, said, "We are very pleased to have received approval from The Austrian Agency for Health and Food Safety (AGES) to initiate our first human study with 3K3A-APC. Our extensive preclinical studies into the neuroprotective effects of 3K3A-APC suggest that it is a promising candidate for the treatment of ischemic stroke."

Stroke, which occurs when blood flow to a part of the brain stops, is the fourth-leading cause of death and the leading cause of adult disability in the United States. A stroke occurs when blood flow in the brain is interrupted, cutting off part of the brain from oxygen. Some brain damage happens immediately, but even when blood flow is restored, brain cells continue dying for hours or days.

According to the American Stroke Association, the Food and Drug Administration-approved tPA (tissue plasminogen activator) is the best treatment for stroke caused by a blocked artery, but to be effective, it must be administered within three hours after symptoms start. If given outside that three-hour window, tPA has shown serious side effects in animal and human brains, including bleeding and breakdown of the brain's protective barrier.

Generally, according to the American Stroke Association, only three to five percent of those who suffer a stroke reach the hospital and satisfy relevant criteria in time to be considered for tPA treatment.

When Griffin's hematology lab and Zlokovic's neuroscience lab began collaborating more than a dozen years ago, activated protein C (APC) was known to stop the growth of blood clots and reduce inflammation, and was being tested for the treatment of adult severe sepsis.

By 2003, their collaborative work pointed to a previously unsuspected ability of APC to directly prevent programmed cell death in the brain, which had emerged as a key to reducing the effects of stroke. The team found that APC dramatically decreased the cellular signals that convince brain cells to kill themselves after a stroke and boosted the cellular signals that persuade the cells to survive.

However, APC's natural blood-thinning properties posed a potential problem to using APC as a treatment for stroke, possibly inducing bleeding in the brain. In response to this challenge, the Griffin lab (including Scripps Research scientists Laurent Mosnier and Andrew Gale) produced an engineered version of APC.

"The protein normally is an anticoagulant," Griffin explained. "We separated out the beneficial effects of the protein acting on cells from this anticoagulant activity. This was done by protein engineering of the 3K3-APC variant to lose most of its anticoagulant activity while retaining its direct actions on cell signaling."

Further work from the team on the engineered 3K3A-APC lent support to the decision to proceed with clinical trials. Large-scale production of this biologic drug, 3K3A-APC, was accomplished by ZZ Biotech with the guidance of Griffin and Thomas Davis, who is a distinguished professor of pharmacology at the University of Arizona.

The journal *Stroke* published a paper by Zlokovic, Griffin, and colleagues, showing the results of giving the federally approved stroke treatment tPA—alone and in combination with 3K3A-APC—to mice and rats four hours after onset of ischemic stroke. The team also gave 3K3A-APC for three consecutive days after stroke and measured the amount of brain damage, bleeding, and motor ability of the rodents up to seven days afterward.

The researchers found that, under those conditions, tPA therapy alone caused bleeding in the brain and did not reduce brain damage or improve motor ability when compared to the control. The combination of tPA and 3K3A-APC, however, reduced brain damage by more than half, eliminated tPA-induced bleeding, and significantly improved motor ability.

"We have developed something that not only counteracts the bleeding, but also reduces brain damage and significantly improves behavior after stroke," said Zlokovic. "I feel very strongly that this approach will extend the therapeutic window for tPA."

ZZ Biotech, founded by Zlokovic with USC benefactor Selim Zilkha, launched the first clinical trials in humans for 3K3A-APC under the supervision of a leading stroke trialist, Professor Patrick Lyden, chair of the Department of Neurology at Cedars-Sinai Medical Center, Los Angeles.

The new Phase 1 study is a randomized, double-blind, placebo-controlled, single-center trial that will investigate the safety and pharmacokinetics of single and multiple ascending doses of 3K3A-APC in healthy adult volunteers. Approximately 62 eligible adult subjects have been assigned sequentially to 1 of 10 cohorts, at successively higher single doses, followed by successively higher multiple doses. Results of the study are anticipated in the first quarter of 2013.

"We are excited by the prospect of one day putting 3K3A-APC in doctors' hands to help reduce the tremendous suffering caused by stroke," said Joseph Romano, chief executive officer of ZZ Biotech.



Professor John Griffin

Team Identifies 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."

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



Associate Professor
Kirill Martemyanov

Memory loss, CONTINUED

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.

Jan Caldwell: A Loyal Contributor to the Fight Against Breast Cancer

Jan Caldwell, the Public Affairs Officer for the San Diego County Sheriff's Department, is a breast cancer survivor since 2002, and she tears up when talking about the experience. "Life has never been the same after that," she said.

Jan went through chemotherapy, radiation, and surgeries at Scripps Health and has been healthy ever since. During her treatments, Jan realized that medical research played a vital role in saving her life.

Soon after she was diagnosed, Jan began making financial contributions to Scripps Research – these gifts have accumulated into a remarkable string of over a hundred gifts dating back ten years. And she spreads the word of the work of Scripps Research to her friends and family every chance she gets. Indeed, many of her gifts are in tribute to friends and family members who have also faced breast cancer.



Jan Caldwell

"Once I got through the treatments, I realized that the next chapter is finding a cure," said Jan. "I wanted to find an entity that did research in breast cancer and was unlocking the secrets of cancer, leading to advances in breast cancer research. Scripps Research was right here locally and had an excellent reputation."

"Every day, I meet someone who has either been stricken by cancer themselves or who has someone in their family who has had cancer," Jan continued. "I am so enormously grateful, as is the patient community, to the Scripps Research scientists who are working towards a cure for this horrible disease. They work so hard, are so intelligent, and have the drive to succeed. My message to them is to keep on trying. My hope is that my humble gifts will lead to a cure. They are making great strides."

Jan, who golfs regularly with a group of pals, recently hosted a golf tournament with the proceeds benefiting Scripps Research.

She also recently joined the Scripps Health Board of Trustees. "I jumped at the chance to serve," she said. "The marriage of research and clinical care is so important. I'm extremely grateful to Scripps Research and Scripps Health for all that they have done for me and are doing for the patient community."

Jan is the public face of the San Diego County Sheriff's Department. She joined the department as its Public Affairs Officer in 2006. She is responsible for the oversight of the Office

of Public Affairs, publication of the department's annual report, news releases, promotional materials, news conferences, and special events. She is a member of the Sheriff's Executive Management Team and advises the Sheriff and Command Staff on matters involving media relations.

She was the steady voice who updated a crush of media and volunteers on the 2010 search for missing Poway teenager Chelsea King, whose body later was found along a trail at Lake Hodges. That same year, she reassured hundreds of anxious Escondido residents that they were okay, despite the discovery of a large cache of volatile explosives in their neighborhood and the need to burn the house down where they were stored.

"Every day is different, and that's the best part of it," said Jan. "I love government service and I always feel for the victims. I've had a great time and would do it again in a heartbeat."

Jan retired as a Special Agent from the Federal Bureau of Investigation in 2006, but was hired by her former FBI colleague, San Diego County Sheriff Bill Gore, soon after her retirement. During her 32-year career with the FBI, she was assigned to the San Diego, San Francisco, and Las Vegas divisions and worked on a variety of general criminal investigations. She was the chief spokeswoman for the San Diego office of the FBI for over a decade—the person TV viewers would most often see when the FBI cracked a big case. She also worked in the Ottawa, Canada and Bern, Switzerland Legal Attaches, and was a crisis/hostage negotiator.

Jan came to the role of local FBI spokeswoman reluctantly. "I was volunteered for it," she said. She eventually grew comfortable in the role, and couldn't pass up the Sheriff Department job offer when it came up.

With the FBI, she responded to New York City after the downing of TWA Flight 800, Oklahoma City after the bombing of the Murrah Federal Building, and the Pentagon after the 9/11 terrorist attacks.

The popular television series "The FBI," stoked her desire to become a crime-fighter.

"Efram Zimbalist, Jr.," she said, recalling the show's star, "always appealed to me."

Jan is a member of the Board of Directors of San Diego County Crimestoppers. She has taught hostage negotiation, undercover techniques, crisis response and media relations at the FBI Academy in Quantico, Virginia.

She holds a Master of Science in Organizational Management and a Bachelor of Science in Clinical Abnormal Psychology, both from the University of LaVerne.

Jan credits much of her success to her father, a Federal Aviation Administration test pilot, who instilled strict discipline in her life.

Jan enjoys playing the violin, although she doesn't expect to join the San Diego Symphony anytime soon. She also loves travel, photography, spending time with family, and gardening.

Jan Caldwell is one of Scripps Research's most loyal contributors. Her steadfast determination to battle breast cancer through medical research is an inspiration.

Joel Buxbaum: Closing in on Treatments for Alzheimer's and Cardiac Diseases

> “Discovery consists of seeing what everybody has seen and thinking what nobody has thought.”

That quote from 1937 Nobel prize winner Albert Szent Gyorgi was fixed to the refrigerator in the New York City apartment of Scripps Research Professor Joel Buxbaum as an intellectual guidepost for his children while they were growing up. “While it is applicable to almost any field of human endeavor, it is a constant reminder that what we accept as ‘conventional wisdom’ in science may not be correct as we pursue our studies of age-related human diseases,” according to Professor Buxbaum.

Professor Buxbaum pointed out that normally the shapes of various molecules that interact in the processes of life fit together in a particular fashion to carry out their functions in the cell or animal. The shapes of the molecules, also referred to as their conformations, have a certain degree of flexibility. When they change their shape or lose that flexibility, for whatever reason, proteins do not interact as well and in some instances behave as poisons, compromising the ability of cells and tissues to function. It is clear that aging increases the prevalence of protein abnormalities and his work is devoted to discovering how time does its damage, the nature of the damage, and by understanding the process and the products, develop ways to insure a longer healthier lifespan.

By using an integrated approach encompassing genetics, animal models, protein chemistry, cell biology, and experimental pathology, Joel has gained insight into a subset of diseases associated with the aging process.

He has long studied cardiac amyloidosis, a common cause of heart failure in the elderly that can be strongly influenced by one's genetic makeup. He and his colleagues have found that a particular mutation in the gene encoding transthyretin, a normal human blood protein, is found in almost 4 percent of African-Americans and results in heart disease in almost all the carriers after age 60. In this disease, as in other disorders produced by transthyretin mutations, the mutant proteins acquire an unusual shape so that the individual molecules stick together forming tiny thread-like aggregates in the heart. These insoluble molecular clumps eventually lead to chronic heart failure with a lingering death and/or an irregular heartbeat which can cause sudden death. His laboratory was able to distinguish the genetic form in African-Americans from senile systemic amyloidosis, which has been found in autopsy in as many as 20 percent of Caucasian men over age 80.

“We refer to the condition in the elderly as ‘Alzheimer's of the heart,’” said Joel. Although the two abnormal amyloid forming proteins are different, the processes share some similarities. However the beta protein responsible for Alzheimer's disease never affects

the heart and the transthyretin protein that forms fibril deposits in cardiac amyloidosis are almost never found in the brain.

His laboratory also described other transthyretin mutations some of which cause disease late in life while others can result in death before age 30. They also developed transgenic mouse models of both wild type and mutant transthyretin deposition in tissues and have recently published studies performed in the model suggesting that normal liver function is required to prevent transthyretin fibril formation in the heart, a phenomenon Joel has called “chaperoning at a distance.” Those studies also identified a set of changes that occur in the heart in response to the amyloid deposits and may be associated with resistance to deposition. More mechanistic molecular studies of the process are being pursued in collaboration with the Wiseman and Kelly laboratories at Scripps Research.

Joel's move to Scripps Research from the Department of Medicine at New York University School of Medicine resulted from a shared interest in transthyretin diseases with Professor Jeffery Kelly. In the late 1980's, one of Joel's postdoctoral fellows at NYU attended an amyloid meeting in Japan. He returned and told him that “You really ought to meet this fellow Jeff Kelly since his thinking about the transthyretin amyloidoses is just like yours.” During the same period, Jeff had heard at other meetings that he should talk to Joel Buxbaum about the biology of these disorders. A bit later when Joel was in Texas visiting his daughter, he called Jeff and arranged to meet in his laboratory at Texas A&M. That meeting initiated a collaboration that facilitated the early analysis of the transgenic mouse models of transthyretin deposition. In early 1999, after Jeff had been at Scripps Research for two years, he introduced Dr. Buxbaum to the late Professor Ernest Beutler, chairman of the Department of Molecular and Experimental Medicine which resulted in his move to Scripps Research.

Joel came to Scripps Research to strengthen his working relationship with Jeff and increase the rate of progress toward understanding the transthyretin diseases. Over the ensuing decade, Professor Kelly and his colleague Professor Evan Powers developed tafamidis, a compound that could inhibit transthyretin amyloid formation in the test tube. The drug was licensed to FoldRx Pharmaceuticals, which carried out a clinical trial leading to the drug's approval by the European Medicines Authority for the treatment of early transthyretin amyloidotic polyneuropathy. The company was subsequently acquired by Pfizer Pharmaceuticals. Joel served as a consultant to FoldRx during the development of the drug and continues to serve as a consultant to Pfizer in their efforts to determine its efficacy in cardiac amyloidosis related to transthyretin deposition.

For the last five years, the Buxbaum laboratory has been pursuing an apparent paradox. There is no question that transthyretin is an

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amyloid precursor forming amyloid deposits in the hearts, nerves and kidneys of both humans and transgenic mice. There is no question that Alzheimer's disease is also a form of amyloidosis that is localized to the brain but the precursor is an entirely different protein, called Aβeta. Despite the fact that both proteins can cause amyloid deposition, albeit of different chemical composition in different locations, over-expressing normal human transthyretin in mice carrying a human Alzheimer's gene prevents the brain damage and behavioral abnormalities seen when only the human Alzheimer's gene is present.

A series of experiments have suggested that nerve cells, which normally do not produce transthyretin, increase its production in the presence of the Alzheimer's disease protein as an apparent nerve cell defense mechanism. Joel and his colleagues have found that transthyretin can be found in a complex with the Alzheimer's protein in some human Alzheimer's patients as well as in the brains of mice producing the human Alzheimer's protein. They have also shown that in the test tube, transthyretin can prevent the formation of the form of the Alzheimer protein that produces nerve cell loss and dementia.

The laboratory is currently studying the molecular pathways whereby nerve cells control the production of transthyretin in response to a number of stresses and to determine whether the pathway may be used therapeutically in humans with Alzheimer's disease.

"These observations were very surprising and certainly counter-intuitive, that a protein that makes tissue compromising amyloid deposits in one circumstance can be an amyloid inhibitor in another, even in the same mouse. I guess it made us think what no one has thought," said Joel.

Last year, Professor Buxbaum was selected as an Ellison Medical Foundation Senior Scholar in Aging. The award provides significant support to allow the development of new, creative research programs by established investigators who may wish to develop new research programs in aging. "I'm privileged to be in the company of group of outstanding senior scientists who have also received this award in the past and in the current class of awardees," said Joel.

Throughout the four-year project, Joel and his colleagues will be working on a project titled, "Defining the Genetics of Body Temperature and its Relationship to Human Longevity." The work was stimulated by the observations of Scripps Research Professor Bruno Conti and Tamas Bartfai, former Chairman of the Molecular Integrative Neurosciences Department at Scripps Research, who noted increased longevity in mice genetically programmed to maintain lower-than-normal body temperatures. The possibility that higher body temperatures over a lifetime may be one of the factors that predispose proteins to misfold and aggregate, placing more stress on the mechanisms that defend cells from the toxic effects of misshapen molecules, was consistent with the other studies on the effects of aging on misfolded proteins ongoing in the Buxbaum laboratory.

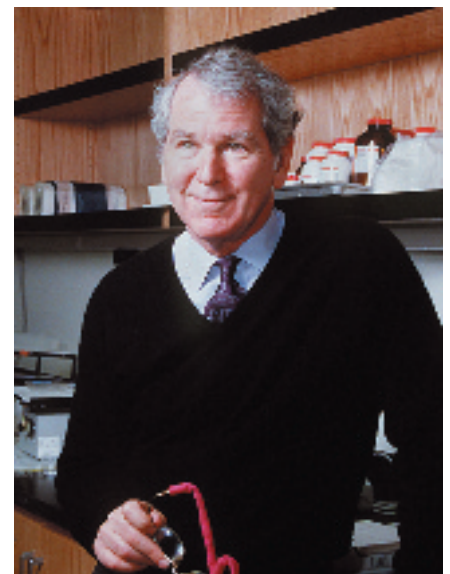
Joel's research has also been supported by the W.M. Keck Foundation, the Skaggs Foundation, the Fidelity Foundation, and The Stein Fund. "Private philanthropy has been extremely helpful to us," said Joel. "It is frequently much more flexible than our basic support from the National Institutes of Health."

"Still, we could do so much more if we had even more private support, as federal funding is getting increasingly difficult to obtain. We're interested in testing at least four other proteins that may behave like transthyretin in defending neurons against protein aggregation in animal models – this work could have ramifications for Alzheimer's disease, Parkinson's disease, prion diseases, and Huntington's disease. Each demands a set of animal models which are expensive, as well as the back-up chemical and molecular biology to understand the mechanisms and exploit them therapeutically. We'd like to expand, particularly into Parkinson's disease, where our initial results have been suggestive."

Joel credits the institutional environment at Scripps Research (as well as the particular interactions with scientists like Professors Kelly and Bartfai) with greatly facilitating his own discoveries.

"Everyone here is smart – they know things that I don't know, complementing my own work and areas of expertise. As opposed to academic medicine, with its complicated multiple missions of patient care, education, and research, here at Scripps Research, you are free to concentrate on your research. The obligation here is to turn out data that will have an impact. In a lecture earlier this year, Tamas Bartfai summed it up when he said 'we have a moral imperative to develop treatments for disease.'"

"Scripps Research is an entrepreneurial and ambitious community with vast expertise in biomedical science – and a great and fun place to work," Joel continued. "It is the only place I have ever worked where the non-technical personnel, from the people in human resources to the environmental staff that maintains our buildings, believes and articulates the notion that they are here to help us turn out data. Such a place demands maximum effort from its scientists and deserves maximal support from the community."



Professor Joel Buxbaum

Gerald F. Joyce Elected to American Academy of Arts & Science



Professor Gerald F. Joyce

Gerald F. Joyce, Scripps Research Institute professor and member of The Skaggs Institute for Chemical Biology, has been elected to the American Academy of Arts and Sciences, one of the nation's most prestigious honorary societies and a leading center for independent policy research.

In addition to Joyce, the 203 fellows and 17 foreign honorary members inducted this year include Secretary of State Hillary Rodham Clinton, Pulitzer Prize-winning playwright and screenwriter Neil Simon, Melinda Gates of the Bill and Melinda Gates Foundation, American film icons Clint Eastwood and Mel Brooks, composer Andre Previn, and Amazon founder Jeffrey Bezos.

In the lab, Joyce and his group work to understand how Darwinian evolution at the molecular level helps to shape the living world. The team has developed methods for carrying out evolution in a test tube, with the goal of developing compounds with practical benefit.

In addition to Joyce, 16 other members of the Scripps Research faculty are fellows of the American Academy of Arts & Sciences.

Also a member of the National Academy of Sciences (NAS), Joyce's most recent honors include the NAS Stanley Miller Award.

The academy's class of 2012 was inducted at a ceremony in October at the academy's headquarters in Cambridge, Massachusetts.

Takayuki Ota Wins HIV Research Award

Scripps Research Institute Assistant Professor Takayuki Ota is one of 12 grant recipients in the international research program, "Creative and Novel Ideas in HIV Research" (CNIHR), sponsored by the International AIDS Society in collaboration with the National Institutes of Health (NIH) and the Centers for AIDS Research.

CNIHR aims to promote innovative research and novel ideas from early-stage investigators whose primary focus has been in fields of scientific inquiry other than HIV.

"The studies supported in this grant program span from basic to clinical science on HIV and its associated comorbidities and co-infections," said Jack Whitescarver, director of the NIH Office of AIDS Research. "This research has the potential to produce an immediate impact, as well as to lead to future advances in AIDS research."

Ota works with the Burton and Nemazee labs. His CNIHR research project is titled "Rapid characterization of NABs in vivo using HoxA10 expanded HSC."

Graduate Student Wins Found Animals Foundation Award

Owen Siggs, graduate student in the Scripps Research Kellogg School of Science and Technology Skaggs-Oxford Program, has won a 2012 Michelson Graduate Student Challenge award, sponsored by the Found Animals Foundation, a Los Angeles-based nonprofit dedicated to reducing euthanasia of pets in shelters.

Funded by Gary Michelson, an inventor of surgical devices and retired orthopedic surgeon, the program provides \$15,000 cash awards for top scientific proposals to develop permanent, nonsurgical sterilants for dogs and cats.

Siggs' proposal, which won in the "Depot Formulation" category, outlines an approach to block a key fertility hormone for the lifetime of the animal.

Making the Most of Your Year-End Giving

> With the end of 2012 right around the corner, it's not too late to take the right steps and make the most of your gifts to support Scripps Research

Cash – The simplest way to make a gift to Scripps Research 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 plannedgiving.scripps.edu.

Bequest – Establish a bequest in your will or trust that reflects your most personal and important lifetime concerns. Bequests to charities are the most popular and widely used planned gifts because a bequest can be changed, costs you nothing as long as you live, and provides an estate tax deduction equal to the value of gifts to charity.

Retirement Plan Assets – Add The Scripps Research Institute as a beneficiary designation to your qualified retirement plan. Scripps Research'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).

Critical Tax Changes in 2013. Be Prepared.

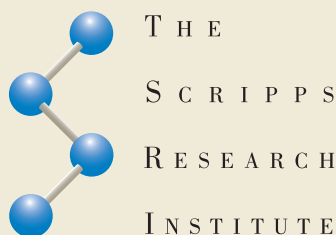
Over the past decade, Congress has passed a series of laws that significantly lowered the federal income tax. Those laws were extended for two years in 2010. However, the new sunset date of January 1, 2013 is fast approaching for what are now called the "Bush tax cuts."

It is important to note that Congress could pass a new tax law that extends some or all of these tax cuts. But until Congress acts, it pays to be aware of what is currently scheduled to happen next year. The changes will affect income tax rates, capital gains tax rates, exemption amounts, itemized deductions, and much more.

In addition, keep in mind that nearly every year, Congress renews a series of temporary tax exemptions and deductions also known as "tax extenders." These typically include higher Alternative Minimum Tax exemptions and the ability to direct tax-free distributions to charity from individual retirement plans (also known as the IRA charitable rollover). As 2012 comes to a close, we encourage you to stay in touch with your advisors, and to contact us if we can be of help.

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 gagraham@scripps.edu.

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