INSTITUTE UPDATE

Scripps Research Institute Chemist Phil Baran Named MacArthur Fellow

Chemist Phil S. Baran of The Scripps Research Institute (TSRI) has won a 2013 MacArthur Fellowship, sometimes called a “genius grant.”

Baran, who is a professor at TSRI and an alumnus of TSRI’s graduate program, will receive a $625,000 fellowship over five years from the John D. and Catherine T. MacArthur Foundation. The grant comes with no specific obligations or reporting requirements.

“Phil is an extraordinary chemist,” said Michael A. Marletta, president and CEO of TSRI and himself a 1995 recipient of a MacArthur Fellowship. “It is very difficult to transform a mature discipline like chemistry but Phil has done this and done it in a very short period of time. His intellect, drive and creativity exemplify chemistry at The Scripps Research Institute. All of us at Scripps are

continued on page 6

RESEARCH UPDATE

TSRI Scientists Create Extremely Potent and Improved New Derivatives of Successful Anticancer Drug

Scientists at The Scripps Research Institute (TSRI) have found a way to make dramatic improvements to the cancer cell-killing power of vinblastine, one of the most successful chemotherapy drugs of the past few decades. The team’s modified versions of vinblastine showed 10 to 200 times greater potency than the clinical drug. Even more significantly, these new compounds overcome the drug resistance that emerges upon treatment relapse, which renders continued or subsequent vinblastine treatment ineffective in some patients.

The TSRI researchers expect that similar modifications will boost the effectiveness of vincristine, a closely related drug that is commonly used against childhood leukemias and Hodgkin’s disease.

“These new compounds should improve on what are already superb anticancer drugs,” said Dale L. Boger, who is the Richard and Alice Cramer Professor and Chair of the Department of Chemistry at TSRI. Boger and members of his laboratory reported the discovery in a paper recently published by the journal *ACS Medicinal Chemistry Letters.*
Scripps Florida Scientists Detail Critical Role of Gene in Many Lung Cancer Cases

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown that a well-known cancer-causing gene implicated in a number of malignancies plays a far more critical role in non-small cell lung cancer, the most common form of the disease, than previously thought. These findings establish the gene as a critical regulator of lung cancer tumor growth. This new information could turn out to be vital for the design of potentially new therapeutic strategies for a group of patients who represent almost half of non-small cell lung cancer cases.

In the study, published by the journal Cancer Research, the scientists found that presence of known oncogene Notch 1 is required for survival of cancer cells. In both cell and animal model studies, disabling Notch 1 leads to a rise in cancer cell death.

“While Notch signaling has emerged as an important target in many types of cancer, current methodologies that target that pathway affect all members of the Notch family, and this has been associated with toxicity,” said Joseph Kissil, a TSRI associate professor who led the study. “We were able to identify Notch 1 as the critical oncogene to target, at least in a common form of lung cancer.”

The new findings show that Notch1 is required for initial tumor growth, as it represses p53, a well-known tumor suppressor protein that has been called the genome’s guardian because of its role in preventing mutations. The p53 protein can repair damaged cells or force them to die through apoptosis—programmed cell death.

Using animal models, the study shows that inhibition of Notch1 signaling results in a dramatic decrease in initial tumor growth. Moreover, disruption of Notch 1 induces apoptosis by increasing p53 stability—substantially increasing its biological half-life, for example.

These findings provide important clinical insights into the correlation between Notch1 activity and the poor prognosis of non-small cell lung cancer patients who carry the non-mutated form of the p53 gene. “If you look at lung cancer patient populations, Notch signaling alone isn’t a prognostic indicator, but if you look at p53-positive patients it is,” Kissil said.

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As we usher in 2014, make it your resolution to check out our improved planned giving website and Discover the Benefits of Giving Wisely at www.plannedgiving.scripps.edu. There you will find a useful resource of ideas and information on how you can support our world class research at The Scripps Research Institute through estate and charitable planning, calculate your tax deduction for charitable gifts, read inspirational stories of people like you that have supported TSRI with charitable planning, and much more.

Of course, if you would like to contact us directly, we would be happy to help assist 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.
TSRI Scientists Discover a New Type of Protein Modification that May Play a Role in Cancer and Diabetes

Scientists at The Scripps Research Institute (TSRI) have discovered a new type of chemical modification that affects numerous proteins within mammalian cells. The modification appears to work as a regulator of important cellular processes including the metabolism of glucose. Further study of this modification could provide insights into the causes of diabetes, cancer and other disorders.

“It appears to be an intrinsic feedback mechanism in glucose metabolism, but I suspect that its other functions throughout the cell will prove at least as interesting when they are more fully elucidated,” said Benjamin F. Cravatt, chair of the Department of Chemical Physiology, member of the Skaggs Institute for Chemical Physiology at TSRI, and professor in TSRI’s Dorris Neuroscience Center.

The Cravatt laboratory has long studied the natural chemical modifications that can change the functions of proteins “on the fly,” switching their biological activities on or off or otherwise altering them. The better known of these modifications include phosphorylation, the addition of a phosphate group, and acetylation, the addition of an acetyl group.

In search of new protein modifiers, Cravatt and Raymond E. Moellering, whose postdoctoral fellowship is sponsored in part by the Howard Hughes Medical Institute and the Damon Runyon Cancer Research Foundation, decided to investigate a small molecule known as 1,3-bisphosphoglycerate (1,3-BPG). The molecule’s chemical makeup suggested that it might readily react with some proteins to form semipermanent, function-altering modifications. 1,3-BPG is one of the main “intermediate” molecules produced during glycolysis, which is a core metabolic pathway that converts glucose to cellular fuel.

“1,3-BPG’s intrinsic reactivity seemed odd to us, considering that it is such a central metabolite,” remembered Moellering.

Moellering’s initial test-tube experiments showed that 1,3-BPG does indeed react with certain lysine amino acids to modify GAPDH, the enzyme that mediates the production of 1,3-BPG. “That gave us the first indication that this reaction does happen, and that we should therefore start looking for it in cells,” he said.

Bestselling “Rizzoli & Isles” Author Tess Gerritsen Raises More than $50,000 for Alzheimer’s Research at TSRI

Tess Gerritsen

Author Tess Gerritsen has raised more than $50,000 to support Alzheimer’s research at TSRI, rallying 385 donors to give over $28,000 and personally contributing $25,000 in matching funds. The bestselling creator of the “Rizzoli & Isles” suspense series launched the War on Alzheimer’s campaign in memory of her father, who died from the disease.

“We are deeply grateful to Tess and everyone who participated in her thoughtful and creative fundraising campaign,” said Michael A. Marletta, president and CEO of TSRI. “The support will enhance our innovative Alzheimer’s research program and help us find new ways to fight this terrible disease.”

Gerritsen’s War on Alzheimer’s campaign spanned two months and raised funds through an online raffle. Two grand prize-winning donors won the opportunity to name characters in Gerritsen’s next “Rizzoli & Isles” novel, set for release in 2014. Andrea Pearson, an author from Lehi, Utah, and Douglas Dorow of Minneapolis, Minn., who lost his mother to Alzheimer’s, will submit their names to Gerritsen.

“Watching my father lose his identity, as he struggled with Alzheimer’s, devastated our family and created a deep fear of memory loss in me. So I sought – through this campaign – to support those heroic scientists battling this terrifying disease. And I truly believe we are close to a cure,” said Gerritsen. “Inviting donors to name characters in my upcoming novel brought us together around this important cause, and I imagine it will be fun for the winners to see their ‘names’ chatting with Jane and Maura on the page!”

SCRIPPS RESEARCH INSTITUTE
The human brain is exquisitely adept at linking seemingly random details into a cohesive memory that can trigger myriad associations—some good, some not so good. For recovering addicts and individuals suffering from post-traumatic stress disorder (PTSD), unwanted memories can be devastating. Former meth addicts, for instance, report intense drug cravings triggered by associations with cigarettes, money, even gum (used to relieve dry mouth), pushing them back into the addiction they so desperately want to leave.

Now, for the first time, scientists from the Florida campus of The Scripps Research Institute (TSRI) have been able to erase dangerous drug-associated memories in mice and rats without affecting other more benign memories. The surprising discovery, published by the journal *Biological Psychiatry*, points to a clear and workable method to disrupt unwanted memories while leaving the rest intact.

“Our memories make us who we are, but some of these memories can make life very difficult,” said Courtney Miller, a TSRI assistant professor who led the research. “Not unlike in the movie *Eternal Sunshine of the Spotless Mind*, we’re looking for strategies to selectively eliminate evidence of past experiences related to drug abuse or a traumatic event. Our study shows we can do just that in mice — wipe out deeply engrained drug-related memories without harming other memories.”

New Findings from The Scripps Research Institute Could Help Improve Development of Drugs for Addiction

Scientists from the Florida campus of The Scripps Research Institute have described findings that could enable the development of more effective drugs for addiction with fewer side effects.

The study, published in the August 2, 2013 issue of the *Journal of Biological Chemistry*, showed in a combination of cell and animal studies that one active compound maintains a strong bias towards a single biological pathway, providing insight into what future drugs could look like.

The compound examined in the study, known as 6′-guanidinonaltrindole (6′-GNTI), targets the kappa opioid receptor (KOR). Located on nerve cells, KOR plays a role in the release of dopamine, a neurotransmitter that plays a key role in drug addiction. Drugs of abuse often cause the brain to release large amounts of dopamine, flooding the brain’s reward system and reinforcing the addictive cycle.

“There are a number of drug discovery efforts ongoing for KOR,” said Laura Bohn, a TSRI associate professor, who led the study. “The ultimate question is how this receptor should be acted upon to achieve the best therapeutic effects. Our study identifies a marker that shows how things normally happen in live neurons—a critically important secondary test to evaluate potential compounds.”

While KOR has become the focus for drug discovery efforts aimed at treating addiction and mood disorders, KOR can react to signals that originate independently from multiple biological pathways, so current drug candidates targeting KOR often produce unwanted side effects. Compounds that activate KOR can decrease the rewarding effects of abused drugs, but also induce sedation and depression.

The new findings, from studies of nerve cells in the striatum (an area of the brain involved in motor activity and higher brain function), reveal a point on the KOR signaling pathway that may prove to be an important indicator of whether drug candidates can produce effects similar to the natural biological effects.

“Standard screening assays can catch differences but those differences may not play out in live tissue,” Bohn noted. “Essentially, we have shown an important link between cell–based screening assays and what occurs naturally in animal models.”
Scripps Research Institute Scientists Reveal How Deadly Ebola Virus Assembles

Scientists at The Scripps Research Institute (TSRI) have discovered the molecular mechanism by which the deadly Ebola virus assembles, providing potential new drug targets. Surprisingly, the study showed that the same molecule that assembles and releases new viruses also rearranges itself into different shapes, with each shape controlling a different step of the virus’s life cycle.

“Like a ‘Transformer’, this protein of the Ebola virus adopts different shapes for different functions,” said Erica Ollmann Saphire, Ph.D., professor in the Department of Immunology and Microbial Science at TSRI. “It revises a central dogma of molecular biology—that a protein molecule has one shape that predestines one biological function.”

“These findings open doors to developing new drugs against Ebola,” added Zachary Bornholdt, Ph.D., senior staff scientist and first author of the study. “Drugs to block viral replication could target any of the structures themselves or the intermediate steps in the structural transformation process.”

Ebola hemorrhagic fever is one of the most virulent diseases known to humankind. Very few pathogens prove more dangerous than Ebola virus once a person is infected. There is no cure, and the case-fatality rate can be up to 90 percent, depending on which strain is involved.

Ebola virus and its cousin Marburg virus are spread when people come into contact with the bodily fluids of a person or animal who is already infected. Infection causes rapidly progressing high fever, hemorrhage and shock. No drugs or vaccines are yet available for human use. Currently, the standard treatment consists of administering fluids and taking protective measures to ensure containment, such as isolating the patient and washing sheets with bleach.

Once rare, the viruses are now reemerging with increasing frequency, and have caused at least four outbreaks among humans in the last two years. Although the viruses are found most often in Africa, they have been unintentionally imported into the United States and Europe several times, and in recent years a version of the Ebola virus has been found replicating in swine raised for human consumption in Asia.

The results of the study, five years in the making, revealed the Ebola VP40 protein exists as a dimer, not as a monomer as previously thought, and it rearranges its structure to assemble filaments to build the virus shell or “matrix” to release countless new viruses from infected cells. The study showed the protein also rearranges itself into rings in order to bind RNA and control the internal components of the virus copied inside infected cells.

This “shape-shifting” or “transformer” behavior explains how the Ebola virus can control a multi-step viral lifecycle using only a very limited number of genes.

AWARDS AND HONORS

Geoff Graham Receives Professional Philanthropy Honor

Geoff Graham, Director, Planned Giving and Estates, in The Scripps Research Institute (TSRI) Philanthropy Department, was named Outstanding Development Professional by the San Diego chapter of the Association of Fundraising Professionals (AFPSD). The honor recognizes effective, creative and ethical leadership in professional fundraising, as well as a commitment to voluntary service and financial support of nonprofit organizations.

Graham, who holds the Certified Fund Raising Executive distinction, develops and arranges planned and major gifts in support of TSRI. He and honorees in seven other categories were spotlighted for their impact on the San Diego community during the AFPSD-hosted 2013 National Philanthropy Day Luncheon, November 7 at the Hilton San Diego Bayfront Hotel.

Professor Erica Ollmann Saphire

Geoff Graham
Richard L. Stone: Turning a Childhood Disability into a Lifetime of Humanity

As a young child, Rick Stone injured his leg and ineffective surgeries left him limping and on crutches for years. The crutches are long gone and Rick is now a highly competitive tennis player. He also graduated from Columbia Law School where he was a Law Review editor and went on to work for some of the most prestigious law firms in New York.

Having been lead counsel on several successful major consumer and securities class action suits, Rick is now in a position to help others. “I want to share my luck with other people...other people work just as hard and are not that lucky.” Together with his wife Lesley Blackner, an environmental lawyer, Rick has had a profound impact in the community. Most recently, Lesley and Rick created the Stone Family Fellowship on the Florida campus of The Scripps Research Institute. The Fellowship supports the development of a young scientist involved in the discovery of novel therapeutics for unmet medical needs.

The recipient is Dr. Vinh Lam, a research associate in the laboratory of Professor Patrick Griffin, Chairman of the Department of Molecular Therapeutics. Dr. Lam is focusing on the development of a new class of anti-diabetic compounds for the treatment of diabetes mellitus (Type-2 diabetes).

Diabetes has not touched the Stone family, but Rick has a deep appreciation for the potential to make progress against this disease that impacts approximately 25 million people in the US alone and is the seventh leading cause of death in the nation. “I like supporting a new medical innovation with mass application that could potentially help millions of people,” said Rick. “There is no better place to make a philanthropic investment in medical research and human health than The Scripps Research Institute. All of us in the community are very lucky to have such a world class institution in our own backyard.”

Baran, continued

very proud of him and I personally am very happy to call Phil my colleague.”

“This is a wonderful recognition of Phil’s remarkable accomplishments and future things yet to come,” said Dale Boger, who is the Richard and Alice Cramer Professor and Chair of the Department of Chemistry at TSRI. “We are thrilled for Phil—he is the real deal.”

MacArthur Fellowships are awarded to individuals who have shown extraordinary originality and dedication in their creative pursuits and a marked capacity for self-direction. Individuals cannot apply for the award; they must be nominated. Typically, 20 to 30 fellows from a wide variety of fields are selected each year.

Baran’s contributions have been in the area of synthetic organic chemistry, where he has pushed boundaries with innovative solutions to synthetic problems. With members of his team at TSRI, he has developed new techniques that dramatically reduce the time, complexity and cost of synthesizing natural products with pharmaceutical potential for conditions including cancer, heart disease and vision loss.

Baran, a graduate of NYU (1997) and TSRI (2001), joined the TSRI faculty in 2003 after a National Institutes of Health-funded postdoctoral fellowship at Harvard University in the laboratory of Nobel Laureate E. J. Corey. Baran is the author of more than 100 papers and an interactive textbook, The Portable Chemist’s Consultant: A Survival Guide for Discovery, Process, and Radiolabeling available from iTunes. He is also co-founder of Sirenas Marine Discovery.

One of the nation’s largest independent foundations, the MacArthur Foundation supports creative people and effective institutions committed to building a more just, verdant, and peaceful world. In addition to selecting the MacArthur Fellows, the Foundation works to defend human rights, advance global conservation and security, make cities better places and understand how technology is affecting children and society.
Tell us about your research and what diseases it impacts.

My work relates to neurodegenerative diseases like Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, the transthyretin amyloidoses, ALS, and prion diseases. Specifically, my laboratory studies how proteins move inside neurons, specialized cells that are very long and involved in memory. This transport is needed to transmit information from one end of the neuron to the other end, over distances that sometimes span a meter in length. The smooth operation of this “cargo transport system” within neurons is essential for neuronal health and is carried out by proteins called molecular motors, which grab cargoes and “walk” on “tracks” inside neurons. If the “tracks” and communication are blocked, the neuron becomes dysfunctional.

This dysfunction is hypothesized to contribute to the neurodegeneration seen in Alzheimer’s and related diseases. A striking feature in all these types of diseases is a swelling of axons in affected neurons, as if blockages of normal transport routes have led to buildups of undelivered molecules. While my lab at TSRI is just two years old and pretty “young,” we’re making progress, which may ultimately mean that we can ameliorate these defects by enhancing transport inside neurons and alleviating the blockages observed in neurodegenerative diseases. There has been a lot of effort put into coming up with therapies for Alzheimer’s across the world, but there has not been a single success story thus far. We’re coming up with a new way of thinking about neurodegeneration in looking at the neuronal transport system. We’re planning on doing some small molecule and genetic high throughput screening in the next year with the intent of inhibiting the blockages and swellings observed in neurons of patients with neurodegenerative maladies.

This is a great time for studying brain diseases. We are hopeful over the next few years that we will identify clues as to what’s happening with these diseases so that we might develop new treatments.

What motivates you?

The possibility of really trying to figure these diseases out. The basic science behind finding their mechanism gives us the power to come up with therapeutics that will affect people’s lives.

What brought you to TSRI?

I finished my postdoctoral work at the University of California, San Diego (UCSD) two years ago. I was looking for a faculty position and TSRI was at the top of my list. I was familiar with TSRI from my work at UCSD, but interviewing here gave me the opportunity to really see and sense the level of collaboration here, which is incredible, as well as the intellectual resources of our people. There are no barriers here. Already in two years, I’ve been able to accomplish the critical activities I wanted to, plus I’ve been able to open up some new possibilities. It’s so easy to do engaging and risky research here with potential rewards in terms of human health—anything is possible.

I understand that philanthropy has been integral to your work. How so?

Philanthropy has been instrumental to establishing my laboratory and to our research. The potential clinical implications of my research was brought to the attention of Arnold and Arlene Goldstein whose philanthropy supports the study of neurodegenerative diseases. The Goldstein’s had already funded an assistant professorship here, and their generosity and vision made it possible to create my position at TSRI. Part of my work is dedicated to the development of the next generation of drugs to battle diseases of interest to the Goldstein’s and I am honored to have their support.
Chris Claiborne: From La Jolla to Boston to Tokyo—Making Strides in Breakthrough Cancer Therapies

A part of one of the first graduating classes of TSRI’s doctoral program in 1996, Chris Claiborne has gone on to dedicate his career to developing cancer therapeutics. Seventeen years later, the humble Claiborne is now Head of the Oncology Drug Discovery Unit for Takeda, with 270 people in his group.

After graduating from Wesleyan University, Chris came to TSRI in 1991. “It was an extremely unique opportunity to be part of a program being built from the ground up,” said Chris. “That and its world-class faculty made my decision to relocate a pretty easy one.”

Under the direction of his advisor, Professor K.C. Nicolaou (now at Rice University), Chris was part of the project team at TSRI that achieved the total chemical synthesis of one of the most significant chemotherapeutic agents known, Taxol, a substance originally isolated from the Pacific Yew tree. The achievement had far-reaching implications for the field of anti-cancer therapeutics.

Chris was one of 20 students who received their doctoral degrees here in 1996. “While TSRI didn’t have the classical campus feel, its research element was very intense and focused,” said Chris.

Already a rising star in graduate school, Chris spent six years “in training” with Merck’s discovery corps before jumping in 2002 to become a Project Leader for Millennium Pharmaceuticals, then a promising startup in the Boston biotech cluster. The move to Millennium worked out well.

Chris was responsible for several first-in-class oncology compounds that moved into clinical trials. “That was the first time I had to advocate for something transforming for the company – but knowing it might fail,” Chris recalled. “Having the organization believe in my arguments transformed my interest in working in biotech.”

Takeda bought Millennium in 2008, and this past May, Takeda and Millennium became an integrated unit. Takeda Boston, as it is now known, combines the innovative science of a leading American biopharmaceutical company with the global assets of Japan’s largest pharmaceutical company. The firm is focused exclusively in oncology to improve the treatment of cancer around the world. Its pipeline has more than 15 oncology investigational compounds that target a broad range of cancers, including lymphomas, lung cancer, and ovarian cancer.

Its flagship oncology therapy, VELCADE® is a type of chemotherapy that is approved by the FDA for the treatment of multiple myeloma. Since its approval, VELCADE has been used to treat an estimated 350,000 patients worldwide. The firm’s other major drug is Lupron, which is prescribed for the treatment of advanced prostate cancer.

“We’re making great strides and are very devoted to breakthrough therapies,” said Chris. “We tend to pick extremely difficult projects. Our belief is that the next leaps in cancer therapies will be initiated by novel biology.”

Chris spends one week a month in Japan. “I’m amazed by the diversity of talent between our two research sites in the U.S. and Japan,” Chris said.

When asked if his experience at TSRI had helped in his career, Chris replied, “Definitely. The amount of attention our small early class at TSRI received from the faculty made it special. That same attention wouldn’t have happened anywhere else.”

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