TSRI Achieves 4-Star Rating from Charity Navigator for Third Consecutive Year

The Scripps Research Institute has achieved Charity Navigator’s coveted 4-star rating for sound fiscal management and commitment to accountability and transparency for the third consecutive year. Only 9 percent of charities rated by Charity Navigator have received at least three consecutive 4-star evaluations, indicating that TSRI outperforms most other charities in America.

“As the nonprofit sector continues to grow at an unprecedented pace, savvy donors are demanding more accountability, transparency and quantifiable results from the charities they choose to support with their hard-earned dollars,” said Ken Berger, President & Chief Executive Officer of Charity Navigator. “Charity Navigator’s goal is to provide donors with essential information needed to give them greater confidence in the charitable choices they make.”

“Receiving four out of a possible four stars indicates that TSRI adheres to good governance and other best practices that minimize the chance of unethical activities and consistently executes its mission in a fiscally responsible way,” said Berger. “This exceptional designation from Charity Navigator differentiates TSRI from its peers and demonstrates to the public it is worthy of their trust.”

Charity Navigator is the leading charity evaluator in America. It is estimated that last year Charity Navigator influenced approximately $10 billion in charitable gifts.

Kenan Charitable Trust Extends Support of Scripps Florida Education Outreach Programs with $1 Million Grant

The William R. Kenan, Jr. Charitable Trust has awarded Scripps Florida $1 million to support the institute’s education outreach programs in Palm Beach County. The grant represents the largest single gift to date in support of Scripps Florida’s education outreach efforts.

Building upon seven years of Kenan Trust support, the new four-year grant will run through May 2017 and fund established programs that reach hundreds of students and teachers each year.

The funding will also enable the development of new programs, including Spanish-language science lessons for middle school students and a hands-on workshop for middle school teachers.

“As Scripps Florida has grown, so has our capability to reach more students and teachers and connect them with our research scientists,” said Deborah Leach-Scampavia, director of education.
Create a Legacy at TSRI Through Your Will or Trust

Each issue of Scripps Discovers highlights the critical work of our researchers that leads to important scientific breakthroughs. You can make a difference by leaving a legacy gift to The Scripps Research Institute. By including us in your will or trust, you can help us continue to achieve critical scientific breakthroughs and further promote our mission.

You may use this sample language:

I give (amount or percentage) to The Scripps Research Institute, a nonprofit corporation, tax identification number 33-0435954, headquartered at 10550 North Torrey Pines Road, La Jolla, California, 92037, to support [insert designation, campus or general use] at The Scripps Research Institute.

If you need more specific language or have any questions, contact Geoff Graham, Director, Planned Giving and Estates at (858) 784-9365 or (800) 788-4931, or by e-mail at gcgraham@scripps.edu. You’ll also find useful planned giving information at our website, plannedgiving.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.
The discovery offers a fresh batch of possible therapeutic targets as well as new diagnostic tools with the potential to predict and inhibit the spread of cancer (metastasis) in patients suffering from the disease.

The research, published recently in *The Journal of Biological Chemistry*, was conducted by TSRI Professor Donald G. Phinney, a nationally recognized authority in the study of adult bone marrow-derived stem cells, and a postdoctoral fellow in his laboratory, Christopher L. Haga.

In the new study, the scientists found that a cluster of seven microRNAs (miRNA) function cooperatively to repress a process known as epithelial-to-mesenchymal transition (EMT). While EMT is part of the normal biology of cell development in some parts of the body, the process has recently been implicated in two dangerous aspects of tumor growth—tumor metastasis and the growth of drug-resistant cancer stem cells.

MicroRNAs are tiny fragments of RNA found in all mammalian cells. They bind to messenger RNAs, a process that generally results in gene silencing. This cluster of miRNAs, located in a genetic region known as DLK1-DIO3, suppresses a specific signaling network in human cancers that primarily affect glands such as breast cancer.

“These results establish the DLK1-DIO3 miRNA cluster as a critical checkpoint regulating tumor growth and metastasis,” said Phinney. “Our data shows that when this cluster is silenced, it accelerates tumorigenesis and proliferation by inducing EMT.”

Silencing the DLK1-DIO3 genetic region is an early event for tumors, Phinney said, pointing out that micro-metastasis can be detected even in the early stages of breast cancer.

One of the seven miRNAs highlighted in the new study—MiR-544—appears to be potent in its powers of inhibition, repressing cancer cell proliferation by inducing Ataxia telangiectasia mutated (ATM), a protein involved in stopping the cell cycle once DNA damage is detected.

“What’s interesting is that MiR-544 blocks cell growth in every tumor cell line we’ve put it into, so we’re looking at it as a potential therapeutic target,” Phinney said.

Phinney noted that dozens of miRNAs exist in the same genetic region. “It’s possible there are other clusters that work together to affect tumor growth and metastasis,” he said.

Kenan, CONTINUED

outreach at Scripps Florida. “The generous support we’ve received from the Kenan Charitable Trust has allowed us to turn that capability into a reality, and we see every day the difference it makes in the lives of young people. We’re extremely grateful for the Kenan Trust’s continued support and are looking forward to many more years of programs dedicated to inspiring the scientists of tomorrow.”

Scripps Florida’s outreach programs include: six-week summer research internships for Palm Beach County high school students and science teachers; 10-week summer internships for college undergraduates; science career panels and laboratory tours for high school classes; “Science Saturday” and “Neuroscience Saturday” daylong workshops for Title I high school students; three-day “InSPIRE” teacher workshops for high school science teachers; and the annual “CELLebrate Science with Scripps Florida” community science festival held inside The Gardens Mall in Palm Beach Gardens.

Professor Donald Phinney
Dale, the Chair of TSRI’s Chemistry Department, is internationally recognized for his multi-faceted work in structure based drug design, organic synthesis, medicinal chemistry, natural products total synthesis, and combinatorial chemistry. He focuses on how chemical approaches can assist in going after biological targets.

“Dale is an outstanding scientist with vision,” said Michael Marletta, President of TSRI. “I am excited to work with him as we move chemistry ahead. It’s unique to have a chemistry department within a biomedical research institute and it’s an essential part of TSRI. Dale is the right leader for the future.”

“We have a fabulous program and a remarkably distinguished group of faculty,” said Dale. “We are working to ensure the department's continued ascent as the premier program in the country. TSRI is the only research institute that has a chemistry program that is so centrally integrated into the foundation of its science.”

TSRI has been highlighted in a Science Watch survey of “high-impact” papers in chemistry as the top institution worldwide by citations per paper. And, according to U.S. News & World Report, the institute’s graduate program is rated seventh overall in the nation in chemistry, with a ranking of third in the specialty of organic chemistry and fourth in biochemistry.

Dale’s own research at TSRI took flight in 1992 as a single jagged peak on an instrument readout that would dramatically reshape decades of research for Dale and his colleagues here. Studies of oleamide, the compound represented, which is critical in controlling the mysterious role of sleep, would lead to potential new treatments not only for sleep, but also for pain relief.

More importantly, the research would help reveal an untapped class of enzymes that, while still largely unexplored, offers potential routes to treatments aimed at just about all known afflictions. Late last year, Dale and Ben Cravatt, a TSRI chemical biologist, Chairman of the Department of Chemical Physiology, and a Professor in the Dorris Neuroscience Center, launched a new company to commercialize the drugs they create at TSRI to manipulate these enzymes.

Such efforts are just one facet of an overall program aimed at studying and exploiting the chemistry of compounds with substantial medical potential. Dale’s team has long distinguished itself as capable of building some of the most complex molecules ever synthesized in the laboratory, and then going on to make tactical chemical improvements that may well save lives in the long run.

Dale, who grew up in Kansas, was always fond of chemistry, in no small part because it came easily to him. As an undergraduate majoring in chemistry at the University of Kansas, he found it fascinating how chemical principles could be used to understand events in biology. “That’s what I always wanted to do,” said Dale.

As his academic training progressed, eventually taking him to Harvard for his PhD in chemistry, he discovered a great love for building molecules. “There was a feeling of accomplishment associated with it that I just loved,” said Dale.

Dale later returned to the University of Kansas, moved to Purdue University, and in 1990, joined the faculty at TSRI, when TSRI introduced chemistry into its labs – in fact, Dale was one of the original seven chemists at TSRI.

“I liked the challenge of starting a new program, conducting chemistry at the biology interface,” said Dale. “TSRI was, and still is, a great setting.”

Decades later, he’s still at it, and still doing much to achieve that sense of accomplishment. And it all started with that critical jagged peak on the readout in 1992. It was identified as part of a study by another scientist at TSRI at the time to help identify compounds that control the poorly understood process of sleep. Dale, who had moved to TSRI in 1990, identified oleamide with Ben Cravatt, and together they deciphered its chemical structure.

Years of collaborative research followed with Richard Lerner, who was TSRI’s former president, and Cravatt, who was just starting out as a graduate student at TSRI at the time.

The work led to the discovery that oleamide builds up in cerebrospinal fluid in rodents as they grow tired. The more oleamide that accumulates, the sleepier you get.

Dale and his colleagues wondered if there might be a way to
control oleamide levels as a sleep aid. His lab began working to figure out oleamide’s structure, and in parallel the researchers were studying just what controlled oleamide breakdown.

The answer was an enzyme originally called oleamide hydrolase but now known as fatty acid amidase hydrolase (FAAH). Beyond offering an interesting glimpse into the chemistry of sleep, the discovery also offered great medical potential—much more than the researchers could have realized at the time.

If FAAH’s activity could be at least partially blocked, Dale and his colleagues reasoned, then this would prevent oleamide breakdown, raising levels and helping to induce sleep. This led to a long quest for compounds that would have just such an effect.

Interestingly, there is something similar in the oleamide cycle in how we feel pain. After an injury, the body releases anandamide, a natural pain killer. In time, the body breaks anandamide down and a subject of research has been to look to slow that process to kill pain.

It became clear that Dale and his colleagues’ work in FAAH could potentially apply to pain management as well as sleep control.

Ultimately, Dale and others at TSRI would identify and produce a range of FAAH inhibitors that continue to show great promise in regulating pain and sleep, and that Dale and Ben’s new company, Abide, will be pushing toward clinical trials.

By controlling natural cycles, these potential drugs offer major benefits over currently available treatments that often have unwelcome side effects. Most sleep aids, for instance, are central nervous system (CNS) depressants that essentially knock a patient out. “You lose all the benefits of what is called physiological sleep,” said Dale, such as the way a day’s memories are processed. And a knocked out patient loses other benefits, such as being able to wake in response to something like a loud noise. Oleamide manipulation simply leads to normal sleep.

Controlling pain and sleep alone are exciting applications of Dale’s career efforts, but those are really just the earliest applications of a much larger discovery. It turns out that FAAH is one of a huge class of more than 250 enzymes known as serine hydrolases. Only a handful of these have been the focus of any targeted drug discovery efforts, and for more than half of the enzymes, researchers don’t even know what they do. Among those at least partially understood are enzymes tied to everything from cancer progression to metabolic diseases. “There’s probably a serine hydrolase involved in almost every sort of physiological process,” said Dale. “It’s more or less an untapped class.”

And with the techniques developed by Dale, Ben, and others, tapping that class has become a much more realistic goal. While it took 15 years to find suitable FAAH inhibitors, scientists can now accomplish the same goals with other enzymes in a tenth of that time.

“We’re very proud of the fact that all of the fundamental science and the discovery of FAAH was accomplished here at TSRI through various internal collaborations,” said Dale. “Today, FAAH is an exciting target for biotechs and large pharmaceutical companies.”

Dale has also found ways to produce countless potential cancer and other kinds of drugs in the laboratory, but another major component of Dale’s work that has spanned multiple decades is research tied to the antibiotic vancomycin. First discovered in 1956, this successful drug is still widely used to treat patients on dialysis and those allergic to certain other antibiotics. But its most important application is in zapping resistant strains of Staphylococcus aureus (MRSA).

Dale became one of the first to ever synthesize the compound in the lab—in 1999, a chemical feat akin to building the Empire State Building. His team went on to synthesize several other compounds in the same group and to develop slightly altered forms of vancomycin, or analogs, in a quest to create versions with significant benefits over the original.

With even the most popular antibiotics such as penicillin, some bacteria developed resistance within a couple of years of initial clinical use. But one of the key reasons Dale has remained intrigued with vancomycin is that it took decades before resistant strains emerged.

When bacteria resistant to vancomycin did finally emerge recently, they pulled this off only through a process known as gene transfer. A few harmful bacterial strains were able to incorporate genes from the bacterium that actually provides vancomycin with a built-in defense against it.

Dale and his colleagues recently successfully reengineered vancomycin to kill the deadliest antibiotic-resistant bacteria. Resistance to vancomycin had become a serious and growing problem in hospitals around the nation and world, and recently in the community at large, raising mortality rates.

Remarkably, Dale’s team has been able to overcome the resistance by replacing a single atom on vancomycin. “It’s unbelievable,” said Dale. “You almost never have a problem where the answer is so crystal clear.”

That one oxygen atom may well mean the difference between life and death for countless future patients. But while changing a single atom may sound simple, creating the altered version actually took about four years. “There is a great feeling of accomplishment when you invest that much time and effort in something then have it work so well,” said Dale.

“Our results have true clinical significance and chart a path forward for the development of next generation antibiotics for the treatment of the most serious resistant bacterial infections,” said Dale. “I am extremely gratified that our results could have the potential to be a great service to mankind.”

“Our vancomycin research illustrates one of the hallmarks of TSRI,” Dale continued. “Most institutions can’t take on making molecules of this complexity, yet we were able to through the seamless collaboration of chemists and biologists—in a traditional university, each group would need to make a major commitment; here it’s a relatively small task for everyone to pitch in.”

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Oxidative stress is a primary villain in a host of diseases that range from cancer and heart failure to Alzheimer’s disease, Amyotrophic Lateral Sclerosis and Parkinson’s disease. Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have found that blocking the interaction of a critical enzyme may counteract the destruction of neurons associated with these neurodegenerative diseases, suggesting a potential new target for drug development.

During periods of cellular stress, such as exposure to UV radiation, the number of highly reactive oxygen-containing molecules can increase in cells, resulting in serious damage.

However, relatively little is known about the role played in this process by a number of stress-related enzymes.

In the new study, the TSRI team led by Professor Philip LoGrasso focused on an enzyme known as c-jun-N-terminal kinase (JNK). Under stress, JNK migrates to the mitochondria, the part of the cell that generates chemical energy and is involved in cell growth and death. That migration, coupled with JNK activation, is associated with a number of serious health issues, including mitochondrial dysfunction, which has long been known to contribute to neuronal death in Parkinson’s disease.

The new study showed for the first time that the interaction of JNK with a protein known as Sab is responsible for the initial JNK localization to the mitochondria in neurons. The scientists also found blocking JNK mitochondrial signaling by inhibiting JNK interaction with Sab can protect against neuronal damage in both cell culture and in the brain.

In addition, by treating JNK with a peptide inhibitor derived from a mitochondrial membrane protein, the team was able to induce a two-fold level of protection of neurons in the substantia nigra pars compacta, the brain region devastated by Parkinson’s disease.

The study noted that this inhibition leaves all other cell signaling intact, which could mean potentially fewer side effects in any future therapies.

“This may be a novel way to prevent neuron degeneration,” said LoGrasso. “Now we can try to make compounds that block that translocation and see if they’re therapeutically viable.”

The work was supported by the National Institutes of Health and by The Saul and Theresa Esman Foundation.

Professor Philip LoGrasso

His team is working now to incorporate alterations discovered by other research teams that may allow them to make a new drug that’s even more potent. Besides adding such a turbocharge, they’re also working modifications that, while not needed for lab tests, would most likely be required for the drug to work in the human body. Then they’ll develop a way to produce the new compound economically. “Now that we’ve overcome that resistance, I think this is an antibiotic that may have a rich and long life still ahead of it,” said Dale.

Dale’s work on both discovering new targets for pain and reengineering vancomycin was partially funded through the generosity and vision of the Skaggs family. “Their funding was instrumental for the fundamental science that allowed us to make the initial discoveries, which were then later supported by the National Institutes of Health,” said Dale. “We’re also grateful for funding we received from Bristol-Myers Squibb that allowed us to translate our discoveries into potential therapeutics.”

In a third area, Dale studies the chemistry of antitumor antibiotics, placing special emphasis on investigations to define the structure-function relationships of natural or designed agents. He and his colleagues have developed a series of compounds that could be wonderful oncology drugs based on a class of molecules he has examined for over twenty years. These compounds have displayed fabulous in vivo efficacy in tumor molecules in animals.

If past history is any indicator, Dale has the scientific fidelity to finish his many skyscraper tasks, however long they take.
Steve Rosenberg: Investing in Pain Research in Honor of Toni

> Steve Rosenberg, a longtime self-employed certified public accountant in the Denver area, is a generous donor to pain research at The Scripps Research Institute (TSRI), in honor of his wife, Toni, who passed away in 2009.

Steve initially gave a small gift to TSRI in memory of Toni, who passed away after receiving a lethal amount of a prescribed pain patch. Toni had undergone back surgery in 2005, which resulted in some complications and she required numerous dangerous opioid medications to deal with the terrible pain she was suffering, including the patch. The opioid medications masked Toni’s pain, but did not eliminate its source, making her pain worse—all of this ultimately contributed to her death four years later.

“Toni’s death was both sad and unnecessary. I wanted to give something back, while honoring Toni, by giving to a charity involved in pain research,” said Steve. “I had heard of TSRI because of its science and was impressed with its high rating on Charity Navigator for efficiency. It means that most of my donation will go to research and won’t be wasted on overhead and marketing. This is very important to me.”

“Because of what happened to Toni, I have an interest in pain management,” continued Steve. “After receiving a nice thank you note for my initial gift from TSRI staff, I was put in touch with TSRI Professor Ben Cravatt, Chairman of the Department of Chemical Physiology and a member of the Dorris Neuroscience Center, who collaborates with both pharmaceutical and biotechnology companies in his work.”

“I reviewed the information on Ben’s fast-track development of natural pain inhibitors in the body that provide therapeutic benefits while avoiding the unwanted, debilitating, and dangerous side effects of most commercial opioid pain drugs, with my neighbor, who is a psychiatrist—he is against the use of pain drugs due to the danger they cause. We were both impressed with the value of Ben’s work – it looks promising. I hope to see some good come from the project so that others will not need to suffer the pain that Toni did. I believe in Ben's project and the hope it provides to people. If he is successful, pain will become more manageable and more people like Toni will not have to die.”

Steve has subsequently made a couple of substantial gifts toward a fellowship in Ben’s lab, the Toni Rosenberg Fellowship, and plans to continue contributing in the future to advance Ben’s pain research and honor Toni.

Steve was born in California. His parents later moved to Colorado. After high school, Steve served in the Air Force. He later graduated from Colorado State University. He spent some time in the real estate industry, and then became a CPA. In his spare time, Steve is also the Treasurer of the Rocky Mountain Churchillians, a group with a high regard for Sir Winston Churchill that shares knowledge and holds programs on his life. He also enjoys golfing, running, and walking.

Toni lives on his memories.

Originally from Utah, Toni graduated with a degree in Communications from the University of Utah with high honors. She later worked in marketing at Mountain Bell which ultimately became Century Link, and subsequently worked for some mining companies in charge of their mainframe computer operations.

Toni belonged to several organizations including Easter Star, a women’s fraternal organization. She also helped several charitable organizations in rewriting their literature – she was great at putting words together that others could not.

Toni and Steve met in 1996, and it was love at first sight. Steve proposed six weeks after they met and they were married in Hawaii in 1997. They were together for over 12 years.

“She was the younger woman,” said Steve. “We were both born in June of 1948, but she was three days younger than me!”

Toni was a voracious reader – she enjoyed novels, history, women’s issues, and current events. She and Steve shared a love of the ocean and loved to travel. Her travels made Toni’s reading come alive. Steve and Toni both enjoyed the beauty of Colorado. She loved art, dance, and classical music. She loved animals and had a couple of cats, one of whom Steve still lovingly cares for. She was vociferous against the unfair treatment of animals.

She was extremely intelligent, had an excellent sense of humor, and loved broadening her knowledge. She was a brave breast cancer survivor.

“Toni had a lovely smile that made me melt,” said Steve. “She is irreplaceable.”

Toni Rosenberg
TSRI staff recently cheered on participants in the 60-mile Susan G. Komen 3-Day for the Cure San Diego event supporting breast cancer research and breast health and education. From a special booth illustrating cancer research efforts at the institute, volunteers handed walkers and runners water, energy bars and pink TSRI wrist bands and shirts. Susan G. Komen for the Cure supports medical research at TSRI. (left photo)

Over 60 participants attended our “Navigating Cancer Research” event held aboard the Emerald Hornblower on San Diego Bay. The attendees enjoyed cocktails and dinner, followed by an enlightening presentation on the latest progress in cancer research from TSRI Associate Professor Peter Kuhn. The event was hosted by Carol Vassiliadis, a major contributor to Dr. Kuhn’s research. Pictured here are TSRI donors Barbara Doren and Kim Doren. Kim is also a member of the Scripps Legacy Society. (top photo)

The dedicated and enthusiastic supporters of Frenchman’s Creek Women For Cancer Research (WFCR) raised an unprecedented $185,000 in 2013 to support postdoctoral fellowships in breast cancer research at Scripps Florida. Over five years, WFCR’s generous contributions now total over $725,000 for research. Pictured (l to r) are Professor Howard Petrie; Kathi Barnhart, BB&T Private Wealth; WFCR leadership Mickey Berman, Marion Wiseman, Anne Stanfield, Helene Shuter, and Irma Blauner; Barbara Suflas Noble, Director of External Affairs; and Associate Professor Kendall Nettles. (bottom photo)

An elegant Night of Celebration was held to honor the Esther B. O’Keeffe Foundation and the O’Keeffe family at the dedication of The Esther B. O’Keeffe Founders Suite at Scripps Florida. With this new gift, the foundation and its trustees become Scripps Florida Founders, a designation that honors those who have made lifetime contributions of $2 million or more to the Jupiter campus. The gift is funding biomedical research and education at Scripps Florida. In this photo, the Hon. Richard A. Gephardt, Chairman of the TSRI Board (left) and Michael Marletta, Ph.D., TSRI President & CEO, stand with Scripps Florida Founder Clare O’Keeffe, trustee of the Esther B. O’Keeffe Charitable Foundation. (right photo)

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- To learn more about supporting TSRI’s cutting-edge research, please contact:

**CALIFORNIA**
(858) 784.2037 or (800) 788.4931
burfitt@scripps.edu

**FLORIDA**
(561) 228.2013
abruner@scripps.edu