# Scripps Florida Funding Corporation

# Annual Report

For the Year Ended September 30, 2020

**Scripps Florida Funding Corporation Annual Report**

**For Year Ended September 30, 2020**

## INTRODUCTION

Florida Statute 288.955 (the "Enabling Statute") created Scripps Florida Funding Corporation ("SFFC") to facilitate the establishment and operation of a biomedical research institution for the purposes of enhancing education and research and promoting economic development and diversity. In addition, the Enabling Statute charged SFFC with the obligation to assure the compliance by The Scripps Research Institute ("TSRI") with the Enabling Statute and the agreement between SFFC and TSRI (the "Operating and Funding Agreement"). The Enabling Statute provides that SFFC shall prepare or obtain certain reports, audits, and evaluations of TSRI's compliance with the performance expectations and disbursement conditions contained in the Enabling Statute. As such, SFFC is submitting this Annual Report to the Governor, the President of the Senate, and the Speaker of the House, as required by the Enabling Statute to be submitted by December 1 of each year.

This SFFC Annual Report addresses the activities and outcomes of SFFC and Scripps Florida ("SF") for the fiscal year ended September 30, 2020 ("Fiscal 2020"). The Scripps Florida Annual Report addressed the activities and outcomes of Scripps Florida for the year ended June 30, 2020, and the information in the Scripps Florida Annual Report was informally updated for this SFFC Annual Report.

The SFFC Annual Report is presented in two parts: first, a summary that highlights the substantial events that have occurred during the year ended September 30, 2020; and second, an itemized report that corresponds with the applicable sections of the Enabling Statute.

**About the Scripps Florida Funding Corporation**

In November 2003, Governor Bush signed into law an historic piece of legislation that laid the framework for The Scripps Research Institute to expand its world-renowned scientific research and endeavors into Florida. The bill, passed by the Florida Legislature during special session, provided a one-time investment of $310 million from federal economic stimulus monies to create Scripps Florida and pay certain expenses for the first seven years, specifically salaries and equipment purchases. In June 2006, The Scripps Research Institute revised the Scripps Florida business plan and SFFC and TSRI revised the scheduled disbursements from the SFFC, which expanded grant funding to December 16, 2013. To oversee the investment and spending of the State's investment in Scripps Florida, the Florida Legislature created the Scripps Florida Funding Corporation, hereto referred to as SFFC, a non-profit entity comprised of a nine-member Board of Directors and one ex-officio member. The role of SFFC was enunciated by Governor Bush: "My vision for this board is that it manages the financial portion of our partnership, but lets Scripps do what it does best – conduct biomedical research."

**SFFC Board of Directors**

Of the nine-member Board of Directors, three Directors are appointed by each of the Governor, House Speaker and the Senate President. Dr. Pamella Dana serves as Chair, and the rest of the Directors are Mr. C. Gerald Goldsmith, Mr. Mark Kasten, Dr. Richard M. Luceri, and Mr. Art Wotiz.

**About Scripps Research**

A leading nonprofit biomedical research institute, Scripps Research is ranked No. 1 in the world by Nature Index for scientific innovation. *U.S. News and World Report* consistently ranks Scripps' graduate school in the top 10 in the United States. The institute's unique structure merges foundational studies in biology, chemistry and computer science with translational research to produce the next generation of drugs and advances in digital and precision medicine. On campuses in California and Florida, scientists in the institute's five academic research departments work hand-in-hand with researchers of the Scripps Research Translational Institute and Calibr, its drug discovery division. Scripps Research trains the next generation of scientific leaders, expands the frontiers of human knowledge and accelerates the development of new medicines to improve lives around the planet. Charity Navigator has rated Scripps Research four stars, its highest rating.

This institution evolved from the Scripps Metabolic Clinic founded by philanthropist Ellen Browning Scripps in 1924, and it now employs more than 2,400 people on its campuses in La Jolla, CA, and Jupiter, FL, where its renowned scientists—including four Nobel laureates and 21 members of the National Academies of Science, Engineering or Medicine—work toward their next discoveries. *US News and World Report* has ranked the graduate program in the Top 10 for 19 consecutive years, and the combined institutions have discovered nine approved drugs to benefit people worldwide. This report references the Florida campus of Scripps Research.

The Scripps Research Florida campus, in the Town of Jupiter in Palm Beach County, Florida, sits on 100 acres adjoining the Florida Atlantic University campus. Three state-of-the-art biomedical research facilities totaling 350,000 square-feet, opened in March 2009 and currently over 500 people are employed there. In addition to the one-time grant from the State of Florida, Palm Beach County provided an economic package that included funding for land and construction of the current permanent facility. For more information, see www.scripps.edu.

## Significant Highlights for the Year Ended September 30, 2020

This section highlights significant scientific and operational news for the Scripps Research Institution for the period of October 1, 2019 through September 30, 2020.

The scientific news includes information on the:

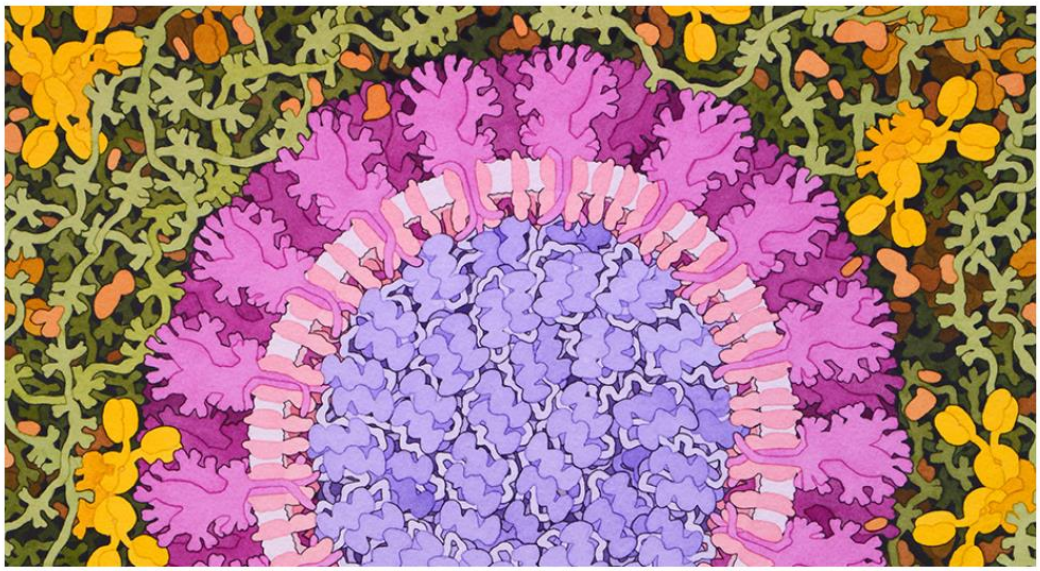
- Research on COVID-19 (p. 4 – 8),
- NIH grant worth $11 million over 8 years (p. 8 – 9),
- American Chemical Society honor to translational medicine pioneer Paul Schimmel (p. 10 – 11), and
- Scripps Research scientists' spots on annual ranking of world's highly cited researchers (p. 11).

The operational news includes information on the:

- Top-ranked graduate program 2020 class (p. 12),
- Women in Science initiative (p. 12 - 13),
- Four-star charity rating (p. 13 – 14), and
- New members of the Scripps Research Board of Overseers (p. 14).

### Scripps Research scientists tackle COVID-19 coronavirus pandemic from many angles

*Ongoing studies revealed important information about how the virus spreads and infects the body, and pointed to different approaches for potential vaccines and medicines.*



Painting by Scripps Research professor David S. Goodsell, PhD*

*This painting, by Scripps* Research professor *David S. Goodsell, PhD, depicts a coronavirus just entering the lungs, surrounded by mucus secreted by respiratory cells, secreted antibodies, and several small immune systems proteins. The virus is enclosed by a membrane that includes the S (spike) protein, which will mediate attachment and entry into cells, M (membrane) protein, which is involved in organization of the nucleoprotein inside, and E (envelope) protein, which is a membrane channel involved in budding of the virus and may be incorporated into the virion during that process. The nucleoprotein inside includes many copies of the N (nucleocapsid) protein bound to the genomic RNA.*

The following question and answer section is based upon a March 2020 report as published in *Nature Medicine.* Scripps Research scientists pursued multiple lines of research aimed at understanding and helping to mitigate the impact of the novel coronavirus behind the COVID-19 epidemic that has spread across the globe. They traced how the virus originated and spreads, explored how it invades the body and how the immune system responds, and worked to develop potential vaccines and medicines against the virus.

**What is coronavirus?** Coronavirus is the family of viruses that causes outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), two illnesses that emerged within the last two decades. Symptoms of coronavirus infections include flu-like symptoms such as fever, cough and shortness of breath. The virus behind the current epidemic, called SARS-CoV-2, is a previously unknown member of the coronavirus family. The epidemic, which began in the Chinese city of Wuhan, has spread to every continent but Antarctica and has sickened tens of thousands of people, resulting in several thousand deaths as of early March 2020.

**How did this virus originate, and how does it spread?** Kristian Andersen, PhD, a Scripps Research genomic epidemiologist and professor in the Department of Immunology and Microbiology, is tracing the origins of the novel coronavirus genome based on public sequencing data. An expert in tracking the spread of deadly viruses (including Ebola, Lassa and Zika), Andersen launched a collaboration with institutes from around the world to analyze the virus's genome and trace its origins. The team's study, reported in *Nature Medicine* on March 17, quells rumors about that it was engineered in a laboratory. Read more about the findings here. His team is also working with colleagues across the globe to better understand how the virus is transmitting in the human population—from its beginning in China to its current spread around the world.

**Can we repurpose existing drugs to treat patients with COVID-19?** Scripps Research teams are testing already approved drugs and compounds with significant safety data in humans available, for activity against SARS-CoV-2. These drugs could be made available to treat coronavirus patients on a much quicker timescale than novel therapies. Calibr, the drug development division of Scripps Research, is leveraging a unique resource, the ReFRAME drug repurposing collection. With support from the Bill & Melinda Gates Foundation, Calibr compiled ReFRAME, the world's leading collection of known drugs comprising over 14,000 compounds that have been approved by the FDA for other diseases or have been tested for human safety. Calibr also developed an open source database containing preclinical and clinical data on these compounds. Since information on the drugs' therapeutic properties and safety is known, they can be screened and rapidly advanced into the clinic. Since its creation in 2018, ReFRAME has been distributed broadly to nonprofit collaborators for global health and used to identify repurposing opportunities for a range of diseases. When the COVID-19 outbreak began, Calibr was able to mobilize ReFRAME quickly to begin searching for existing drugs and other compounds that might be repurposed against the coronavirus. ReFRAME is now being screened to identify compounds that can:

- Prevent the virus from entering and infecting cells
- Prevent the virus from replicating in cells
- Augment the efficacy of antivirals such as remdesivir, which is being tested in five COVID-19 clinical trials

Since the outbreak began, Calibr has established collaborations to screen the ReFRAME library for potential coronavirus therapies with nine outside research teams, including U.S. laboratories in Maryland, Massachusetts, New York, and Texas, as well as overseas labs in the UK, Germany, Belgium and Hong Kong. Calibr is also establishing partnerships with pharmaceutical companies to screen earlier stage antiviral collections against COVID-19. ReFRAME has been highlighted in the COVID-19 Therapeutics Accelerator launched by the Bill & Melinda Gates Foundation.

In addition to Calibr, Matthew Disney, PhD, a chemistry professor the Florida campus of Scripps Research, is also exploring compound repurposing. Disney develops potential medicines that work by precisely targeting disease-causing RNA, the protein-building machinery inside of cells. He is using his tools to identify drug-like compounds that may have activity against the novel coronavirus, which is an RNA virus.

**How does the novel coronavirus interact with our immune system? Can this knowledge help us fight the virus and develop a vaccine?** Researchers in the Scripps Research laboratory of Dennis Burton, PhD, chair of the Department of Immunology and Microbiology, are studying the human immune response to SARS-CoV-2 infections. They are also working to identify potent "broadly neutralizing antibodies," which might serve as the basis for vaccines or antiviral therapies against COVID-19.

The laboratory of Ian Wilson, DPhil, chair of the Department of Integrative Structural and Computational Biology at Scripps Research, is studying the differences between the virus that caused the 2002 outbreak of SARS (SARS-CoV) and the novel coronavirus (SARS-CoV-2) behind the COVID-19 pandemic. They are exploring whether antibodies produced against one coronavirus can interact with a different coronavirus. They found that one antibody (CR3022), previously produced against SARS-CoV by the company Crucell Holland BV, binds to the receptor binding domain on the spike protein of SARS-CoV-2. Wilson's team produced the first 3D structure of the SARS-CoV-2 receptor binding domain bound with the CR3022 antibody that neutralizes SARS-CoV. In another collaboration with the University of Hong Kong, cross reactive antibody responses were found between SARS-CoV-2 and SARS-CoV infection. The Wilson lab plans to work on structures of antibodies isolated from recovering COVID-19 patients when they become available from researchers at medical research centers. The findings of these studies are producing critical information for researchers worldwide as they seek to develop vaccines to SARS-CoV-2.

Andrew Ward, PhD, a professor of Integrative Structural and Computational Biology at Scripps Research, has a longstanding interest in understanding immune responses to coronaviruses, particularly how the body responds to the surface spike protein on the virus. Ward's team revealed the first structure of a human coronavirus spike protein in 2017 from the HKU1 virus, and subsequently went on to describe spike proteins from SARS and MERS—the latter when it was connected with a neutralizing antibody. They are now investigating the structure of the SARS-CoV-2 spike protein and working with collaborators in the United States who are isolating antibodies from infected patients. Lastly, Ward's group has developed new imaging methods that work as a diagnostic tool to directly probe blood samples from infected patients.

**What are approaches being taken to develop novel vaccines against coronavirus?** Scripps Research professors Michael Farzan, PhD, and Hyeryun Choe, PhD, both in the Department of Immunology and

Microbiology, study how the SARS-CoV-2 virus infects cells. Their goal is to develop optimal vaccine approaches, and to advance rapid development of antiviral drugs and biologic therapies. Jiang Zhu, PhD, an associate professor in the Department of Integrative Structural and Computational Biology at Scripps Research, has developed a patented technology for engineering vaccines built with tiny fragments of protein nanoparticles. Zhu and coworkers have developed a self-assembling prototype that features SARS-CoV-2 protein spikes protruding from the protein nanoparticle scaffold that could stimulate a strong immune system response in cells to protect against a real SARS-CoV-2 virus.

**Breaking COVID-19's 'clutch' to stop its spread**

*Researchers engineer RNA-targeting compounds that disable the pandemic coronavirus' replication engine.*

Scripps Research chemist Matthew Disney, PhD, and colleagues have created drug-like compounds that, in human cell studies, bind and destroy the pandemic coronavirus' so-called "frameshifting element" to stop the virus from replicating. The frameshifter is a clutch-like device the virus needs to generate new copies of itself after infecting cells.

> "Our concept was to develop lead medicines capable of breaking COVID-19's clutch," Disney says. "It doesn't allow the shifting of gears."

Viruses spread by entering cells and then using the cells' protein-building machinery to churn out new infectious copies. Their genetic material must be compact and efficient to make it into the cells.
The pandemic coronavirus stays small by having one string of genetic material encode multiple proteins needed to assemble new virus. A clutch-like frameshifting element forces the cells' protein-building engines, called ribosomes, to pause, slip to a different gear, or reading frame, and then restart protein assembly anew, thus producing different protein from the same sequence.

But making a medicine able to stop the process is far from simple. The virus that causes COVID-19 encodes its genetic sequence in RNA, chemical cousin of DNA. It has historically been very difficult to bind RNA with orally administered medicines, but Disney's group has been developing and refining tools to do so over more than a decade.

The scientists' report, titled "Targeting the SARS-CoV-2 RNA Genome with Small Molecule Binders and Ribonuclease Targeting Chimera (RIBOTAC) Degraders," appeared Sept. 30 in the journal *ACS Central Science*. Disney emphasizes this is a first step in a long process of refinement and research that lies ahead. Even so, the results demonstrate the feasibility of directly targeting viral RNA with small-molecule drugs, Disney says. Their study suggests other RNA viral diseases may eventually be treated through this strategy, he adds.

> "This is a proof-of-concept study," Disney says. "We put the frameshifting element into cells and showed that our compound binds the element and degrades it. The next step will be to do this with the whole COVID virus, and then optimize the compound."

Disney's team collaborated with Iowa State University Assistant Professor Walter Moss, PhD, to analyze and predict the structure of molecules encoded by the viral genome, in search of its vulnerabilities. The scientists zeroed in on the virus' frameshifting element, in part, because it features a

stable hairpin-shaped segment, one that acts like a joystick to control protein-building. Binding the joystick with a drug-like compound should disable its ability to control frameshifting, they predicted. The virus needs all of its proteins to make complete copies, so disturbing the shifter and distorting even one of the proteins should, in theory, stop the virus altogether.

Using a database of RNA-binding chemical entities developed by Disney, they found 26 candidate compounds. Further testing with different variants of the frameshifting structure revealed three candidates that bound them all well, Disney says.

Disney's team in Jupiter, Florida quickly set about testing the compounds in human cells carrying COVID-19's frameshifting element. Those tests revealed that one, C5, had the most pronounced effect, in a dose-dependent manner, and did not bind unintended RNA. They then went further, engineering the C5 compound to carry an RNA editing signal that causes the cell to specifically destroy the viral RNA. With the addition of the RNA editor, "these compounds are designed to basically remove the virus," Disney says.

Cells need RNA to read DNA and build proteins. Cells have natural process to rid cells of RNA after they are done using them. Disney has chemically harnessed this waste-disposal system to chew up COVID-19 RNA. His system is called RIBOTAC, short for "Ribonuclease Targeting Chimera." Adding a RIBOTAC to the C5 anti-COVID compound increases its potency by tenfold, Disney says. Much more work lies ahead for this to become a medicine that makes it to clinical trials. Because it's a totally new way of attacking a virus, there remains much to learn, he says.

> "We wanted to publish it as soon as possible to show the scientific community that the COVID RNA genome is a druggable target. We have encountered many skeptics who thought one cannot target any RNA with a small molecule," Disney says. "This is another example that we hope puts RNA at the forefront of modern medicinal science as a drug target."

*The study, "Targeting the SARS-CoV-2 RNA Genome with Small Molecule Binders and Ribonuclease Targeting Chimera (RIBOTAC) Degraders," appears in the journal ACS Central Science. In addition to Disney and Moss, contributors include first authors Hafeez Haniff, Yuquan Tong, Xiaohui Liu, Jonathan L. Chen, Blessy M. Suresh and Raphael I. Benhamou of Scripps Research; and Ryan J. Andrews, Jake M. Peterson and Collin A. O'Leary of Iowa State University's Roy J. Carver Department of Biophysics, Biochemistry and Molecular Biology. The work was funded by the National Institutes of Health as well as NIH/NIGMS grants.*

**Scripps Research chemist earns NIH grant worth $11 million over 8 years**

*Professor Matthew Disney, PhD, applies RNA discoveries to brain diseases, cancer and COVID-19.*

In recognition of his high-impact work advancing the field of RNA-targeting medicines, the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health, has awarded Scripps Research Chemistry Professor Matthew Disney, PhD, a prestigious Research Program Award, to aid Disney's development of treatments for incurable diseases such as Alzheimer's, Parkinson's, ALS and frontotemporal dementia.

The NINDS Research Program Award is designed to enable creative scientists with a proven track record to focus their time and talent on advancing science rather than on writing grant applications. It lasts for five years, is extendable for up to eight, and in Disney's case, is worth up to $11 million cumulatively. This was awarded in May 2020.

> "Matt Disney's work has changed the landscape of what scientists now consider 'druggable targets,' and in the process, reinvigorated research on multiple incurable diseases, including muscular dystrophy, ALS and advanced, metastatic cancer," says Douglas Bingham, executive vice president of Scripps Research. "That this prestigious NIH award program has now gone to two of our Florida-based scientists in four years speaks to the world-class, high-impact biomedical research we do."

In 2017, Florida-based Neuroscience Professor Ron Davis, PhD, was among the inaugural group of 30 scientists to receive the NINDS Research Program Award. Davis studies both basic and applied neuroscience, and has discovered biological mechanisms underpinning memory and forgetting, while searching for new treatments for neurodegenerative diseases. Disney says he plans to use the Research Program Award to advance new treatments for some of the most challenging brain diseases.

> "There are millions of patients and their families that have invested their time and their own tissue samples to advance the development of targeted therapeutics," Disney says. "They are awaiting development of new approaches that can be advanced into medicines for brain and nervous system diseases, such as Alzheimer's, Parkinson's and ALS and multiple rare genetic diseases."

Essential for life, RNA carries out fundamental duties in our cells. It templates genes, builds proteins, and regulates multiple cell activities, including how much of a particular protein gets manufactured from our DNA. Controlling, silencing or repairing RNA, especially toxic RNA that might be garbled, expanded or broken, has been a goal of many scientists through the years. By designing a sort of computational and mathematical decoder, Disney has succeeded against tough odds. RNA is built of simple stuff, just four nucleic acids. Under an electron microscope, it appears more like loose yarn fragments than the large, sweater-like protein structures most drugs reliably target. As a result, many scientists had written it off as an undruggable molecule. By defining those relatively rare, stable RNA structures, and then matching those forms to a database he built of complementary small-molecule drugs, Disney built a system for identifying RNA drugs for multiple diseases. His system has identified compounds now under study as potential disease-modifying treatments for conditions including Fragile X syndrome, muscular dystrophy and inherited ALS. Beyond ALS and muscular dystrophy, Disney's RNA-modifying tools are showing great applicability to cancers and a variety of other rare genetic disorders. In addition, because many viruses are made of RNA, Disney's technology can be used to identify new classes of antiviral drugs. His team is now developing drug candidates to attack the novel coronavirus, SARS-CoV-2, the cause of pandemic COVID-19.

A founder of Expansion Therapeutics in San Diego, CA and Jupiter, FL, Disney has been recognized with the 2019 Raymond and Beverly Sackler International Prize in Chemistry from Tel Aviv University, the 2018 Weaver H. Gaines BioFlorida Entrepreneur of the Year award, and the 2015 National Institutes of Health Director's Pioneer Award.

**American Chemical Society honors translational medicine pioneer Paul Schimmel as a life-changing entrepreneur**

*Schimmel will receive the 2020 Kathryn C. Hach Award for Entrepreneurial Success, which honors those who have used the transforming power of chemistry to improve lives.*

Paul Schimmel, PhD, was named the recipient of the 2020 Kathryn C. Hach Award for Entrepreneurial Success by the American Chemical Society (ACS) in November 2019. The Hahn Professor in the Department of Molecular Medicine at Scripps Research, Schimmel is a world-renowned expert in studying the enzymes and processes involved in correcting errors that can occur in the interpretation of genetic information. The Hach Award recognizes outstanding entrepreneurs who have created commercially viable businesses or products within the chemical enterprise, which have made a positive impact on people and the economy. "Starting with a good idea, sustained by passion, fueled by persistence and hard work, the award recipient created something where nothing existed before," ACS says in a statement.

Schimmel's career-long focus has been on a group of universal enzymes, the 20 aminoacyl tRNA synthetases, which interpret genetic information in all living organisms. Research he published in the early 1980s established the concept of ESTs (expressed sequence tags) and the strategy of shotgun sequencing - work that *Nature* magazine cited as one of the four foundations of the human genome project. He has founded or co-founded multiple biotechnology companies, including Alnylam Pharmaceuticals, Cubist Pharmaceuticals (acquired by Merck and Co.), aTyr Pharma, Abide Pharmaceuticals, Alkermes, Sirtris Pharmaceuticals (acquired by GlaxoSmithKline) and RepliGen Corp. He also was founding director of Momenta Pharmaceuticals.

> "I'm honored to be recognized by the ACS as entrepreneur who has used the transforming power of chemistry to improve people's lives," says Schimmel. "My achievements have been possible because of the many remarkable colleagues in my laboratory and throughout Scripps Research who have helped me turn discoveries into products that improve health. Being able to make that contribution to the greater community will always be my driving force."

Most recently, Schimmel's lab, in collaboration with others at Scripps Research, described an enzyme, $YRS^{ACT}$, that can boost production of blood platelets, which are tiny blood cells that help the body form clots to stop bleeding. The discovery may lead to a future therapeutic for internal bleeding.
In other work, Schimmel and his colleagues at the Ackerman laboratory (University of California, San Diego) identified a protein, ANKRD16, that plays a critical role in ensuring that genes are properly translated into proteins, thus maintaining healthy brain cells. His lab is also making efforts to develop tRNA synthetases to treat diseases such as macular degeneration and cancers.

Schimmel earned his doctoral degree from the Massachusetts Institute of Technology (MIT). He is the author or co-author of 500 scientific publications, as well as coauthor of a widely used three-volume textbook on biophysical chemistry. Schimmel is an elected member of the National Academy of Sciences, National Academy of Medicine, National Academy of Inventors, American Philosophical Society, American Academy of Arts and Sciences, and American Association for the Advancement of Science. He is also cofounder or founding director of numerous enterprises that have developed new medicines arising from academic research.

Schimmel received his award, which is sponsored by the Kathryn C. Hach Award Endowment, at a ceremony on March 24, 2020, in conjunction with the ACS Spring National Meeting in Philadelphia. He received a $20,000 prize and was featured in the official ACS publication, *Chemical & Engineering News.*

**Scripps Research scientists garner 20 spots on annual ranking of world's highly cited researchers**
*The prestigious list identifies scientists who've 'disproportionately' influenced their fields of research over the past decade.*

From world-leading organic chemists to neuroscientists who've expanded the realm of knowledge surrounding addiction and human touch, Scripps Research scientists have landed 20 spots on the 2019 Highly Cited Researchers list. The institute has doubled its presence on the list from five years earlier, when it garnered a still-respectable 10 spots. The annual ranking includes researchers from nearly 60 nations whose studies were among the top 1 percent of most-cited publications in their fields over the prior decade.

> "The Highly Cited Researchers list contributes to the identification of that small fraction of the researcher population that contributes disproportionately to extending the frontiers of knowledge," says David Pendlebury, senior citation analyst at the Institute for Scientific Information. "These researchers create gains for society, innovation and knowledge that make the world healthier, richer, more sustainable and more secure."

This year, the list includes 6,217 Highly Cited Researchers. Among the top 1,000 are McArthur Fellows Phil Baran and Jin-Quan Yu, each of whom has independently transformed the field of organic chemistry. Other Scripps Research scientists on the list include Ben Cravatt, George Koob, Ardem Pataopoutian and Peter Schultz, who is also president and CEO of Scripps Research. The institute is also represented on the list by Robyn Stanfield, John Yates III, Ian Wilson (who is named twice, earning a spot in separate categories for microbiology and immunology), Jeong Hyun Lee, Ryan McBride, James Paulson, William Schief, Andrew Ward, Richard Wyatt and Devin Sok. Noted scientists Jean-Philippe Julien, Michael Hanson and Laura Walker—all former graduate students or post-docs at Scripps Research—are also on the list for work they completed while affiliated with the institute.

The methodology that determines the "who's who" of influential researchers draws on data and analysis from bibliometric experts at the Institute for Scientific Information, part of the Web of Science Group. This year the list includes 6,217 Highly Cited Researchers in various fields from nearly 60 nations. The United States is home to the highest number of Highly Cited Researchers, representing 44 percent of the researchers on the list, followed by China at 10.2 percent.

**Scripps Research awards doctoral degrees to class of 2020, celebrates graduates' diverse scientific accomplishments**

Scripps Research awarded doctoral degrees to 44 graduate students who completed the rigorous academic and research requirements of the institute's Skaggs Graduate School of Chemical and Biological Sciences. The degree recipients comprised the 28th graduating class of Scripps Research's graduate program, and in lieu of the traditional annual commencement ceremony on the La Jolla campus, a virtual celebration for the class of 2020 was held in July in consideration of public health restrictions imposed in response to the ongoing COVID-19 pandemic.

> "We congratulate all of our 2020 graduates on their spectacular journey at Scripps Research, where each of them contributed their boundless energy and passion to expand scientific knowledge and ultimately, improve human health," said Phil Dawson, PhD, dean of graduate and postdoctoral studies at Scripps Research, and a professor in the Department of Chemistry. "Even though we are unable to celebrate our graduates in person this year, it's gratifying to know that so many of these outstanding young scientists are already hard at work investigating potential causes of and treatments for COVID-19 and other diseases that afflict so many."

In addition to the online graduation event this summer, the Skaggs Graduate School featured profiles of its graduates in a "virtual commencement walk" to appear on the Scripps Research website and social media channels. The goal is to engage the greater community in the graduates' diverse areas of biomedical research and career aspirations. Ranked among the top 10 doctoral programs of its kind in the nation by *U.S. News & World Report*, the Skaggs Graduate School of Chemical and Biological Sciences at Scripps Research offers training in chemistry, chemical biology, neuroscience, immunology, cell biology and other biomedical research areas. The program immerses students in intensive laboratory research while offering a customizable course curriculum that allows students to match individual research interests while exploring multidisciplinary topics at the interface of chemistry and biology.

**WISE women scientists welcomed at Scripps Research in Jupiter, Florida**

*Institute launched Women in Science Education (WISE) initiative to support graduate program fellowships with Dec. 3, 2019 kick-off event*

Innovation flourishes in a climate of diversity, and that's the climate at Scripps Research, Florida, where women now number 39 out of the 72 students attending the institute's internationally recognized graduate program, the Skaggs Graduate School of Chemical and Biological Sciences. While women comprise only about one-third of the science workforce around the world, Florida's Skaggs graduate program attracts women doctoral students at a rate of over 54 percent. To build that momentum, the institute's Jupiter campus launched an important initiative: Women in Science Education (WISE). For a limited time, a generous donor has offered a half-million-dollar match to enable a permanent graduate school educational endowment. Scripps Research Florida introduced its WISE program at an on-campus kick-off event on Tuesday, Dec. 3, 2019, at 5:30 p.m., during which complimentary cocktails and hors d'oeuvres were enjoyed by attendees, who were given an overview of the graduate program by Christoph Rader, PhD, associate dean of the graduate program in Florida. In the months that followed, the WISE Committee held a number of philanthropic events, including private dinners, a symposium

aligned with the International Day of Women and Girls in Science, and a first-of-its-kind, family-friendly "science stroll" throughout the Scripps Research campus.

The Skaggs graduate program is small and specialized, widely recognized for its high quality. U.S. News and World Report has ranked it #2 in the nation for biochemistry, #5 for organic chemistry, #6 for chemistry overall and #10 for biological sciences. Students work closely alongside faculty mentors, whose work is changing science and medicine. They include Microbiologist Hyeryun Choe, PhD, who studies why the zika virus causes birth defects when a nearly identical virus, dengue, does not. She found an answer in placental cells, and is now working on new approaches to protect babies.

They also include Biochemist Laura Bohn, PhD, who studies how to create pain relievers with the efficacy of opioids but without the life-threatening side-effects, and Chemist Kate Carroll, PhD, who has discovered why pancreatic cancer is one of the few cancer types that doesn't respond well to a powerful class of therapies called kinase inhibitors. Carroll recently discovered the reason lies in a specific type of chemistry, and is now investigating methods to make those drugs work for thousands of cancer patients. Scripps Research is focused on enabling more talented young women to pursue careers in science, according to Rader. "The graduate program at Scripps Research is a magnet for young scientific talent," Rader says. "It's highly competitive—only 22 percent of more than 800 annual applicants are admitted—and highly popular, partly because the students know they'll be working in our labs alongside our renowned scientists from day one. When they emerge with their doctoral degrees, they'll be equipped with the education and training to make a positive impact on human health."

The WISE committee comprises business leaders from throughout southern Florida. They are: Monique Brechter, former Executive Director of Development, Transmission at NextEra; Michele Jacobs, president and chief executive officer of the Economic Council of Palm Beach County; Karen Marcus, former Palm Beach County Commissioner; Elaine Solomon, founder and co-chair of the PGA National Women's Cancer Awareness Days, and Patti Travis, senior managing director of First Republic Bank. In May of this year, the Skaggs Graduate School conferred doctoral degrees on its largest class in school history, 54 students. According to its statistics, 20 percent of the school's graduates go on to earn tenure-track positions at major universities and research institutes and 33 percent pursue careers in the pharmaceutical and biotechnology sectors.

**Scripps Research Received Highest Possible Charity Rating**

Following a qualitative review of dozens of performance metrics valued by charitable givers, Scripps Research was awarded an "exceptional" rating of four stars, indicating it exceeds industry standards and outperforms most charities in its cause. The four-star designation from Charity Navigator, an independent evaluator, is the highest rating possible.

> "This recognition from Charity Navigator is so important to us because it acknowledges our dedication to financial stewardship," says Jennifer Crosby, vice president of Philanthropy and Community Engagement for Scripps Research. "We're grateful for all of the support we receive from our donors and our community, and they can expect the best from us in return."

Financial gifts to Scripps Research enable scientific discovery that advances the field of medicine, ultimately to improve or save lives. Among the many FDA-approved drugs to result from ingenuity at

Scripps Research are treatments for several cancers, leukemia, arthritis and respiratory distress syndrome. Dozens of additional drug candidates—targeting pain, multiple sclerosis, dementia and other disease areas—are currently undergoing analysis and refinement.

In addition to its reliance on philanthropic gifts and funding from the National Institutes of Health, Scripps Research has established a first-of-its-kind translational research model for funding nonprofit research institutes. Through industry partnerships and licensing agreements, the organization is advancing new drug candidates and bringing yet another layer of financial sustainability to fuel its mission.

> "Being a four-star charity means that when we receive gifts, we put them to the best and most efficient use," Crosby says. "We believe our new operating model will make our organization an even more appealing place for donors to invest in the future of health."

Charity Navigator is the nation's largest and most-utilized evaluator of charities. Its professional analysts have examined tens of thousands of non-profit financial documents to develop an unbiased, objective, numbers-based rating system to assess over 9,000 of America's charities. The ratings help donors gauge how efficiently a charity will use their support, how well it has sustained its programs and services over time, and its level of commitment to accountability and transparency.

**Board of Overseers**

The Board of Overseers, which significantly expands the institute's advisory network, was created at the September 2018 BOD meeting, serves as an "advisory capacity to institute leadership and its Board of Directors regarding academic, scientific and business strategies, as well as provide support for the institute's philanthropic efforts," according to Pete Schultz, president and CEO of Scripps Research. The 21 founding members of the Board include influencers in biotechnology, pharmaceuticals, academia, law, science policy, and investment.

> "We are privileged that so many highly respected and successful business leaders in the field of life science are helping us broaden our impact as a nonprofit scientific institute," says Pete Schultz, PhD, president and CEO of Scripps Research. "More than ever, the world needs innovative science—and a framework that enables great science to be translated efficiently into life-saving medicines."

The newest members of the Board of Overseers are Brian Dovey, a partner at life science venture capital firm Domain Associates, where he has served on the board of more than 35 companies and has been chairman of six; Stacy Kellner Rosenberg, retired attorney, noted philanthropist and former nonprofit leader who is an ardent supporter of science; and Sandford (Sandy) Smith, former executive vice president of Genzyme, CEO of two biopharma companies and a board member of multiple publicly traded biotech companies, where he focuses on commercial strategy.

## Scripps Florida Scientific Publications

Scripps Research performs biomedical research and drug discovery on two campuses, one in La Jolla, California and the other in Jupiter, Florida. The following excerpts demonstrate the scientific publications and news between October 1, 2019 and September 30, 2020 that derived from work on the Florida campus.

### Scientists identify what may be a key mechanism of opioid addiction

*The discovery might lead to better addiction treatments.*

Scientists at Scripps Research discovered a molecular process in brain cells that may be a major driver of drug addiction, and thus may become a target for future addiction treatments. The scientists, who published their discovery on Oct. 22, 2019 in *Cell Reports*, used an advanced imaging technique to visualize brain cell activity during exposure to an opioid, in a part of the brain known to be centrally important for addiction. They found that key brain-cell changes that occur with addiction and help sustain addiction behavior are accompanied by—and plausibly driven by—particular changes in a signaling system involving a messenger molecule called cyclic AMP (cAMP).

> "Our findings suggest the possibility, which we now want to test, that an intervention to reverse these cAMP changes could reduce symptoms of addiction, such as drug cravings and withdrawal dysphoria," says the study's senior author Kirill Martemyanov, PhD, professor and co-chair of the Department of Neuroscience at Scripps Research.

Drug overdoses—most of which involve opioids—kill about 70,000 people in the United States every year, and on the whole, drug addiction or dependency is estimated to affect tens of millions of Americans. Yet, researchers have never found a cure or even a very good treatment for addiction. That is mainly because they have lacked techniques for studying the deep molecular mechanisms in the brain that underlie the addiction process.

Last year, Martemyanov's team—in collaboration with Dr. Ronald Davis' laboratory, also at Scripps Research—developed a tool that could help with such investigations: a sensor system genetically engineered into mice to enable real-time recordings of cAMP levels in any type of neuron. The cAMP molecule functions as an internal messenger in neurons, carrying signals from receptors embedded in the cell's outer membrane into the inner workings of the cell. Until now, this realm of neurobiology has been relatively obscure for scientists.

In the new study, the scientists used their sensor system to track cAMP levels in neurons that make up a brain structure called the nucleus accumbens—a central component of the brain's reward and motivation system, which is essentially subverted by addiction. Opioids, like other drugs of abuse, cause an unnaturally large surge of dopamine into the nucleus accumbens. When this happens repeatedly, reward and motivation processing is altered, and this alteration largely accounts for the behavioral features of addiction—including the buildup of tolerance to the drug so that ever-higher doses are needed, and the drug cravings and dysphoria that occur with drug withdrawal. The researchers wanted to see how cAMP signaling from dopamine receptors on nucleus accumbens neurons change with repeated opioid exposure, and if that could explain the changes to accumbens function.

They also intend to use their cAMP reporter tool to investigate genes that influence susceptibility to opioid addiction. In a related study published recently in *PLoS Biology*, Martemyanov's group showed that a gene linked to a neuropsychiatric disorder called neurofibromatosis type I acts in striatal neurons to boost the rewarding effects of morphine and regulates dopamine signaling to cAMP.

*Authors of the study, "*Allostatic Changes in the cAMP System Drive Opioid-Induced Adaptation in Striatal Dopamine Signaling*," include Brian Muntean, Maria Dao and Kirill Martemyanov, all of Scripps Research, and support for the research was provided by the National Institutes of Health.*

**How to kickstart self-cleaning mode in brain cells? Scientists may have solved the puzzle**

*A surprise discovery from Scripps Research suggests a new target for neurodegenerative disease treatments.*

Neuroscientists at Scripps Research have identified a molecule in brain cells that regulates autophagy, an important cellular waste-recycling system implicated in a range of brain disorders. The new finding illuminates an important feature of nervous system biology and opens the door to new approaches for treating Alzheimer's and other neurodegenerative diseases. In their study, which appeared in *Nature Communications* in November 2019, the scientists show that a protein known as ULK, which is responsible for switching on autophagy in cells, is regulated by an enzyme called RPM-1. Although the scientists did their principal experiments in the simple roundworm *C. elegans*, a prominent model for biology and neuroscience research, tests in human cells suggest that this important relationship could exist in most or all animals.

> "How autophagy is regulated in the brain has remained cryptic, but here—for the first time—we've found a molecule that potentially does just that," says Brock Grill, PhD, at Scripps Research's Florida campus. "There's potential for clinical applications down the road, given the growing evidence that neurodegenerative diseases such as Alzheimer's feature prominent abnormalities in autophagy in nerve cells."

**The importance of tidy brain cells** The autophagy process works as a key waste-disposal and housekeeping system in cells by recycling damaged and potentially harmful proteins and other cellular components. In some animals, calorie restriction and genetic manipulations that extend lifespan have been found to boost autophagy. The process is particularly important in the brain, where most nerve cells cannot be replaced in adulthood and therefore must keep themselves—and their often-lengthy output fibers, called axons—tidy and healthy for many decades. One obvious way to enhance autophagy would be to target a protein that normally inhibits this process. But scientists have suspected that the nervous system might have its own separate regulator of autophagy. That critical molecule is what Grill and his colleagues believe they have uncovered.

**An unexpected finding** At the onset of their study, Grill and his team were not investigating autophagy. His laboratory primarily studies nerve cell development, and the team was doing experiments in *C. elegans* with a molecule called RPM-1, which plays an important role in axon growth and maintenance of nerve cell connections. To their surprise, the researchers found that RPM-1 affects axon development by inhibiting ULK, a known initiator of autophagy, thereby restricting autophagy in the nervous system. He and his colleagues are following up with further experiments to explore the functions of RPM-1 in the nervous system and beginning to explore translating their findings into models of neurodegenerative disease.

*The study's first authors were Oliver Crawley and Karla Opperman of the Grill laboratory. The other Scripps Research authors, besides Brock Grill, were Muriel Desbois, Isabel Adrados, Melissa Borgen and Andrew Giles. One author, Derek Duckett, was previously based at Scripps Research's Florida campus, and is now located at the Moffit Cancer Center in Tampa, Florida. The research was funded by the National Institutes of Health.*

**Protein that polices mitochondria in brain's striatum may underlie Huntington's selective damage, study finds**

Parkinson's, ALS and Huntington's disease all share a curious feature: The genetic mutations underlying the diseases appear in all cells, yet only specific brain regions, or cell types, initially die from those mutations. A new study from Scripps Research published June 2020 online in the journal the Proceedings of the National Academy of Science (PNAS) offers a possible reason for such tissue-specific vulnerability in the case of Huntington's disease. The discovery, from the lab of Scripps Research Neuroscientist Srinivasa Subramaniam, PhD, may offer clues to similarly isolated tissue vulnerability in other degenerative brain diseases, and may point to new therapeutic approaches.

The region of the brain associated with voluntary movement, called the striatum, is under attack in Huntington's disease. Huntington's affects an estimated 1 in 10,000 people in the United States. Its symptoms, including slowness, muscle jerks, loss of coordination, slurred speech and difficulty eating and swallowing, usually appear between ages 30 and 50. There is no treatment.

Subramaniam and his team discovered that in the striatum, a protein called Rhes forms a complex with another protein, Nix, to help maintain the optimal number of mitochondria. In healthy striatal cells, they found that Rhes conducts surveillance of the neurons' mitochondria. In a model of Huntington's, if Rhes detects damaged mitochondria, it moves quickly to recruit factors that engulf and dissolve the organelle. If too many mitochondria are wiped out, however, this leads to neuronal death, and thus a protective cellular mechanism transforms into predator.

> "In normal conditions, all those parts are recycled. But in Huntington's so many mitochondria are lost that the cell just dies," Subramaniam says. Rhes is disproportionately present in the striatum, so "this gives you a possible mechanism for selective vulnerability." Subramaniam adds. "So the next question is, can we target this to prevent the excess removal?"

While Huntington's affects the striatum, in Parkinson's disease, another brain region, the substantia nigra, degenerates first. A next step for his group will be searching for players similar to Rhes that are uniquely overexpressed in that brain region. *The study, "Rhes, a striatal-enriched protein, promotes mitophagy via Nix," was published online at www.pnas.com on Nov. 1, 2019. Besides lead author Subramaniam and first author Sharma, the co-authors include Uri Nimrod Ramirez Jarquin, Oscar Rivera, Melissa Karantzis, Mehdi Eshragi, Neelam Shahani and Vishakha Sharma of Scripps Research, Florida, and Ricardo Tapia of the Universidad Nacional Autonoma de Mexico. This research was partially supported by a training grant in Alzheimer's Drug Discovery from the Lottie French Lewis Fund of the Community Foundation for Palm Beach and Martin Counties. This research was supported by funding from NIH/National Institute of Neurological Disorders and Stroke grant, NIH/National Institute of Neurological Disorders and Stroke grant, and grants from Cure Huntington Disease Initiative (CHDI) Foundation. Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México, also supported the work, in part.*

**New technology allows control of gene therapy doses**

Scientists at Scripps Research in Jupiter have developed a special molecular switch that could be embedded into gene therapies to allow doctors to control dosing. The feat, reported in the scientific journal *Nature Biotechnology* in December 2019, offers gene therapy designers what may be the first viable technique for adjusting the activity levels of their therapeutic genes. The lack of such a basic safety feature has limited the development of gene therapy, which otherwise holds promise for addressing genetically based conditions. The scientists' technique appears to solve a major safety issue and may lead to more use of the strategy.

The Scripps Research team, led by principal investigator Michael Farzan, PhD, demonstrated the power of their new switching technique by incorporating it into a gene therapy that produces the hormone erythropoietin, used as a treatment for anemia. They showed that they could suppress expression of its gene to very low levels with a special embedded molecule, and could then increase the gene's expression, over a wide dynamic range, using injected control molecules called morpholinos that the U.S. Food and Drug Administration has found to be safe for other applications.

> "I think that our approach offers the only practical way at present to regulate the dose of a gene therapy in an animal or a human," Farzan says.

Gene therapies work by inserting copies of a therapeutic gene into the cells of a patient, if, for example, the patient was born without functional copies of the needed gene. The strategy has long been seen as having enormous potential to cure diseases caused by defective genes. It also could enable patients to receive a steady, long-term delivery of therapeutic molecules that are impractical to deliver in pills or injections because they don't survive for long in the body. However, gene therapies have been viewed as inherently risky because once they are delivered to a patient's cells, they cannot be switched off or modulated. As a result, only a handful of gene therapies have been FDA-approved to date. The simplicity of the technique, and the fact that morpholinos are already FDA-approved, could allow the new transgene switching system to be used in a wide variety of envisioned gene therapies, Farzan adds.

Farzan and his colleagues are now working to adapt their ribozyme switch technique so that it can be used as a gene therapy failsafe mechanism, deactivating errant transgenes permanently. *Authors of the study, "*A reversible RNA on-switch that controls gene expression of AAV-delivered therapeutics in vivo*," include Guocai Zhong, Haimin Wang, Wenhui He, Yujun Li, Huihui Mou, Zachary Tickner, Mai Tran, Tianling Ou, Yiming Yin, Huitian Diao, and Michael Farzan of Scripps Research. Funding for the research was provided by the National Institutes of Health.*

**RNA-targeting strategy successfully blocks a vexing driver of Parkinson's disease**

*A new drug-like compound prevents the body from producing a protein that's often at the root of Parkinson's.*

Scientists at Scripps Research have developed a drug-like compound that selectively prevents production of the protein underlying most causes of Parkinson's disease, alpha-synuclein. The study underscores the untapped potential of addressing diseases mediated by "undruggable" proteins via the messenger RNAs that encode them. Published on Jan. 3, 2020 in *Proceedings of the National Academies of Sciences*, the study is authored by Scripps Research chemistry professor Matthew D. Disney, PhD, graduate student Peiyuan Zhang, and their colleagues. If DNA serves as the code of life, genes within DNA provide the code for specific proteins. For a gene to actually encode a protein, however, it must first be transcribed with the help of messenger RNA. The messenger RNA serves as a template for protein production, a process called translation, which is orchestrated by molecular machines called ribosomes. Disney's alpha-synuclein compound, which he named synucleozid, stops the ribosome from detecting the messenger RNA template, thus preventing the translation or "printing" of the alpha-synuclein protein. The Scripps Research team collaborated on the study with a team from Rutgers University led by M. Maral Mouradian, MD, director of the Institute for Neurological Therapeutics.

> "We showed not only that we can inhibit the translation of alpha-synuclein, which is an important protein in Parkinson's disease and dementia, but also that this compound can stop its messenger RNA from being recognized by a ribosome," Disney says. "In other words, the compound doesn't allow the messenger RNA to be made into the alpha-synuclein protein. We believe this unique mechanism is broadly applicable."

Disney has spent more than a decade building technologies capable of identifying drug-like compounds to do this. A system he invented called "Inforna" computationally uses genetic sequence to predict complementary small molecule-RNA interactions. Most drugs on the market work by binding to problematic proteins to limit their ability to cause harm. However, for a drug to bind, those proteins must have stable structures with favorable binding pockets. The alpha-synuclein protein is one example of many in the genome that have confounded scientists' efforts to bind with medications, due to their undefined structure. In fact, the so-called "druggable genome" is currently comprised of only about 3,000 genes out of an estimated 20,000 protein-coding genes. Disney says his research suggests that many undruggable proteins are transcribed by RNA that do have stable structures, meaning the RNA should be druggable, offering an effective workaround.

With an estimated 1 million people in the United States alone living with the condition, at an estimated cost of over $50 billion annually, Parkinson's causes chronic, progressive disability due to the death of dopamine-producing cells in the brain. The symptoms may include slowness of movements, impaired coordination, limb and trunk stiffness, tremor, and eventually dementia and psychiatric manifestations.

The benefit of choosing a small molecule to do this rather than an RNA-binding oligonucleotide is that a therapeutic agent must be very, very small to cross the blood-brain barrier. It must also be selective, and apparently these starting compounds are selective. But Disney notes that this is a proof-of-concept study, and that a long road lies ahead before Synucleozid might become a Parkinson's drug candidate that can move into clinical trials in humans.

*The study, "Translation of the intrinsically disordered protein alpha-synuclein is inhibited by a small molecule targeting its structured mRNA," is published in the Proceedings of the National Academies of Sciences the week of Dec. 30. Besides Disney and Zhang, authors include Hye-Jin Park, Jie Zhang, Eunsung Junn and M. Maral Mouradian of Rutgers Robert Wood Johnson Medical School, and Ryan Andrews, Sai Pradeep Velagapudi, Daniel Abegg, Kamalakannan Vishnu, Matthew Costales, Jessica Childs-Disney, and Alexander Adibekian of Scripps Research, along with Walter Moss of Iowa State University. This work was funded by NIH Grants. Additionally, M.M.M. is the William Dow Lovett Professor of Neurology and is supported by the Michael J. Fox Foundation for Parkinson's Research, American Parkinson Disease Association, New Jersey Health Foundation, and NIH Grants. E.J. is supported by NIH Grants and by the State of New Jersey. Support to the Disney lab from the Nelson Family Fund also aided the research.*

**Compounds protect brain cells' energy organelle from damage linked to Alzheimer's, ALS, Parkinson's**

*Potential medications to protect mitochondria found with novel screening strategy.*

A sophisticated new screening platform developed by scientists at Scripps Research has enabled them to discover a set of drug-like compounds, including an ingredient found in sore throat lozenges, that may powerfully protect brain cells from dangerous stresses found in Alzheimer's and other neurodegenerative diseases. The screening platform, described in a January 2020 paper in *Science Advances*, allows researchers for the first time to rapidly test "libraries" of thousands of molecules to find those that provide broad protection to mitochondria in neurons. Mitochondria are tiny oxygen reactors that supply cells with most of their energy. They are especially important for the health and survival of neurons. Mitochondrial damage is increasingly recognized as a major factor, and in some cases a cause, for diseases of neuronal degeneration such as Alzheimer's, Parkinson's, and ALS.

The scientists, in an initial demonstration of their platform, used it to rapidly screen a library of 2,400 compounds, from which they found more than a dozen that boost the health of neuronal mitochondria and provide broad protection from stresses found in neurodegenerative disorders. The researchers are

now testing the most potent of these mitochondria-protectors in animal models of Alzheimer's, amyotrophic lateral sclerosis, and other diseases, with the ultimate goal of developing one or more into new drugs.

> "It hasn't yet been emphasized in the search for effective therapeutics, but mitochondrial failure is a feature of many neurodegenerative disorders and something that must be corrected if neurons are to survive," says principal investigator Ronald Davis, PhD, professor in the Department of Neuroscience at Scripps Research. "So I'm a big believer that finding mitochondria-protecting molecules is the way to go against these diseases."

Scientists in prior studies have developed screens for molecules that can enhance mitochondrial function, but only by focusing on mitochondria in cells from outside the brain. A screening system that measures mitochondrial health in mature neurons requires cultures of such neurons, which are relatively difficult to maintain—in part because they do not divide to make new neurons. Davis was convinced, however, that only this more difficult approach, which others including pharmaceutical researchers have avoided, would enable the discovery of compounds that protect brain cells by protecting their mitochondria. The screening system developed by Davis and his team uses cultured neurons from mouse brains in which mitochondria are labeled with fluorescent tags. Sophisticated microscope imaging and semi-automated image analysis enables the researchers to quickly record mitochondrial numbers, shapes and other visible markers of health in the neurons before and after exposure to different compounds.

*The authors of the study,* "Neuron-based high-content assay and screen for CNS active mitotherapeutics," *were Boglarka Varkuti, Miklos Kepiro, Ze Liu, Kyle Vick, Yosef Avchalumov, Rodrigo Pacifico, Courtney MacMullen, Theodore Kamenecka, Sathyanarayanan Puthanveettil, and Ronald Davis, all of Scripps Research. Support for the research was provided by the National Institutes of Health, the Lottie French Lewis Fund of the Community Foundation for Palm Beach and Martin Counties, the Coleman Hogan Fund for Memory Research, W. Meyer, A. Dreyfoos, and P. McGraw.*

**Long-term memory performance depends upon Ras gene expression, study finds**

*Suppression of genetic switch boosts hardwired memory in Drosophila.*

Storing and retrieving memories is among the most important tasks our intricate brains must perform, yet how that happens at a molecular level remains incompletely understood. A new study from the lab of Neuroscience Professor Ronald Davis, PhD, at Scripps Research, Florida, sheds light on one element of that memory storage process, namely the storage and retrieval of a type of hardwired long-term memory. The Davis team found that moving memories to long-term storage involves the interplay of multiple genes, a known group whose activity must be upregulated, and, unexpectedly, another gatekeeping gene set, Ras, and its downstream connecting molecules, which are down-regulated. If either Ras or its downstream connector Raf are silenced, long-term memory storage is eliminated, the team writes in the *Proceedings of the National Academies of Sciences,* published the week of Jan. 13, 2020. The type of memory they studied, ironically has a rather difficult-to-remember name: "protein-synthesis dependent long-term memory," or PSD-LTM for short. To study how it and other types of memory form, scientists rely upon the fruit fly, *Drosophila melanogaster,* as a model organism. The genetic underpinnings of memory storage are mostly conserved across species types, Davis explains.

To assess how the flies' memory consolidation process works at a molecular level, they used a process called RNA interference to lower expression of several candidate genes in several areas of the fly brain. Doing so with both the Ras gene and its downstream molecule Raf in the fly brain's mushroom body, its memory-storage area, had a two-pronged effect. While the Ras enzyme, Ras85D, was already known for its roles in organ development and cancer, the studies showed that in the adult brain, it apparently plays

memory gatekeeper, helping direct whether experiences should be remembered as intermediate memory that dissipates after a time, or as long-term "protein-synthesis dependent" memory that persists.
Gating off the memory from the intermediate storage process shifted it over to PSD long-term memory storage, indicates that it's an either-or situation. Intermediate storage appears to be the fly brain's preferential, default pathway, Noyes says. He expects that the neurotransmitter dopamine will prove to play a key signaling role.

> "We believe that dopamine signals to the brain that this memory is important enough to be stored long-term. We speculate that Ras and Raf receive this dopamine signal and thereby block intermediate memory and promote PSD long-term memory," Noyes says. How this "intermediate" memory system works in humans requires further study as well, he adds. "It's becoming apparent that many of the same genes involved in intermediate memory storage also play a role in mammalian memory and plasticity," he notes.

*In addition to Noyes and Davis, the authors of "Ras acts as a molecular switch between two forms of consolidated memory in Drosophila," published the week of Jan. 13, 2020 in PNAS, include Erica Walkinshaw, also of Scripps Research.*

**Editing cancer-causing RNA delivers precision strike on triple-negative breast cancer**

The move toward targeted anti-cancer treatments has produced better outcomes with fewer side-effects for many breast cancer patients. But so far, advances in precision medicine haven't reached people diagnosed with so-called triple-negative breast cancer. An innovative compound developed in the lab of Scripps Research chemist Matthew D. Disney, PhD, offers a new potential route to intervene. Published the week of January 20, 2020 in the *Proceedings of the National Academies of Sciences*, the Disney team's paper describes a compound that, in mice, awakened cancer cells' self-destruct system, killing the cancer cells and stopping their spread, while leaving healthy cells untouched. While most drugs work by binding to proteins, Disney's compound first latches onto an uncommon target, a molecule called a microRNA precursor, involved in silencing gene transcription. Next it recruits and activates the cell's own disposal system to destroy it. MicroRNA-21 has been called an oncogenic RNA because of its role in metastasis. An abundance of it predicts lower survival in triple-negative breast cancer patients.
Triple-negative breast cancer lacks the traits that would make it sensitive to precision anti-cancer drugs currently available. Between 10 and 15 percent of people with breast cancer receive this diagnosis, as their tumors test negative for estrogen and progesterone sensitivity, as well as HER2 protein production, leaving traditional chemotherapy as the first-line treatment.

> "Breast cancer affects one in eight women in their lifetime. Unfortunately, there are no precision medicines for triple-negative breast cancer patients. And often times, these cancers become metastatic—they spread. This metastasis can result in death," Disney says. "We asked ourselves if we could develop a compound that can target genes that cause cancer metastasis and direct triple-negative breast cancer cells to self-destruct."

Disney says a tool he developed in 2014 to identify druggable RNA structures and compounds that would bind to them, called Inforna, revealed the needle in the proverbial haystack, a compound that bound selectively to microRNA-21. Disney's team combined the optimized compound with a second molecule that recruits and activates an RNA-cutting enzyme, one that is part of our immune system. In this way, the compound enabled destruction of the microRNA-21 target.
Disney has dubbed this precision target-and-destroy system "RIBOTAC," short for "ribonuclease-targeting chimeras." The tool represents a sort of gene-expression editor, precisely deleting disease-linked sequence from RNA. Matthew Costales, PhD, one of Disney's graduate students, was the paper's first author. Costales says a variety of cell-based and mouse tests produced expected results. In addition

to triple-negative breast cancer, the team found the compound broadly decreased invasiveness in melanoma and lung cancer cell lines that showed aberrant microRNA-21 activity. It had no apparent effect on healthy breast tissue. Disney says these are early days for a treatment approach that defies convention. Traditional drugs work by binding to proteins because they are structurally more complex than RNA, which has only four bases. The chemistry strategies his team employs overcome that barrier, Disney says.

*In addition to Disney and Costales, the authors of* "Small-molecule targeted recruitment of a nuclease to cleave an oncogenic RNA in a mouse model of metastatic cancer," *include Haruo Aikawa, Yue Li, Jessica Childs-Disney, Daniel Abegg, Dominic Hoch, Sai Velagapudi, Yoshio Nakai, Tanya Kahn, Kye Won Wang and Alexander Adibekian of Scripps Research, plus Eric Wang of the University of Florida and Ilyas Yildirim of Florida Atlantic University. The work was supported by the National Institutes of Health, the American Chemical Society's Medicinal Chemistry Predoctoral Fellowship to Costales, the Nelson Family Fund, the Alan J. and Susan A. Fuirst Philanthropic Fund, and Frenchman's Creek Women for Cancer Research.*

**Autism model links uneven growth of brain regions to excess support cells**

*MRI study of mice with a mutation in the autism risk gene PTEN suggests that early intervention might help affected infants.*

Scientists at Scripps Research have shed new light on a genetic mutation that is clearly linked with autism spectrum disorders; in so doing they have highlighted a potential pathway for early treatment. Mutations in a gene known as *PTEN*—one of the most extensively validated in autism genetics studies—can lead to the disproportional overgrowth of nerve fiber tracts that convey information between brain regions, according to the Scripps Research imaging study of mice that carry the mutation. The research, published February 2020 in *Translational Psychiatry*, points to the likelihood that this abnormal and uneven brain growth is caused by an excess of support cells in the brain, known as glia, during early development. The researchers suspect that such effects might be largely preventable with early drug treatments, thereby correcting the most prominent brain abnormality found in individuals with *PTEN* mutations and autism.

> "These findings suggest that, in principle, one could use brain imaging, together with genetic testing, to detect this syndrome in infants when there is still time for useful intervention," says the study's senior author Damon Page, PhD, associate professor in the Department of Neuroscience at Scripps Research.

The U.S. Centers for Disease Control and Prevention estimates that autism spectrum disorders (ASDs) now affect one in every 37 boys and one in every 151 girls in the country. These disorders are largely genetic, though no one gene mutation dominates. Instead, it appears that ASDs can result from mutations in any of hundreds of different genes, each of which accounts for only a tiny subset of ASD cases. *PTEN* is among the most studied of these risk genes. Mutations that inactivate one copy of the *PTEN* gene can cause autism as well as "macrocephaly"—the overgrowth of the brain and head—in both humans and lab mice. Moreover, the molecular signaling pathways affected by the reduction in *PTEN* activity are known to be disrupted in about 5 percent of ASD cases, including cases without *PTEN* mutations. Scientists therefore hope that studying *PTEN* mutations will yield important clues about the causes of autism and good strategies for treating it.

They found that adult mice with the mutation show a pattern of abnormal brain growth—higher in multiple areas, lower in one or two others including the forebrain—very much like that seen in humans who have *PTEN* mutations and autism. Yet they also found that week-old mutant mice do not show this same pattern; instead they show considerable variability in growth abnormalities across different brain

regions. Moreover, the brains of the mutant mice at this early stage are only moderately different than normal mouse brains. Both of these findings hint that a treatment for humans with *PTEN* mutations, if it were available, could prevent much of the usual brain overgrowth/undergrowth and autism signs if delivered shortly after birth. The scientists now plan to do further studies to find compounds that could have a similar effect at reducing glial cell over-proliferation but would be more suitable for development into drugs. They are also following up with studies in the mutant mice of how overgrowth in different brain regions correlates with different autism-like behaviors.

*The other co-authors of the study,* "Pten haploinsufficiency disrupts scaling across brain areas during development in mice," *were Ori Cohen PhD, Massimiliano Aceti PhD, Aya Zucca, and Jenna Levy, of Scripps Research; and Jacob Ellegood PhD and Jason Lerch, PhD of the Hospital for Sick Children in Toronto. Support for the research was provided by the National Institutes of Health and gift funds from Ms. Nancy Lurie Marks.*

**Insulin signaling suppressed by decoys, scientists find**

*Study presents new direction for research on type two diabetes, insulin resistance, longevity and aging.*

In a discovery that may further the understanding of diabetes and human longevity, scientists at Scripps Research have found a new biological mechanism of insulin signaling. Their study, involving the roundworm C. elegans, reveals that a "decoy" receptor is at work in binding to insulin molecules and keeping them from sending signals for increased insulin production. The study appeared in the February 2020 journal eLife. It describes a new player in the insulin signaling system, one that may offer insights into insulin resistance, a feature of type two diabetes. The scientists are now assessing whether a similar decoy exists in humans. If so, it could present a new target for diabetes treatment and prevention research.

> "This truncated, 'decoy' receptor that we've found adds yet another layer of complexity to our understanding of insulin signaling," says lead author Matthew Gill, PhD, associate professor in the Department of Molecular Medicine at Scripps Research in Florida.

Insulin is a hormone of ancient and fundamental importance to animals, and insulin-like proteins are found even in simpler organisms such as bacteria, fungi and worms. In humans, it acts as a signal to key cell types, directing them to pull in glucose from the blood. This helps maintain cellular energy stores and keeps blood sugar within a safe range. Type 2 diabetes, which is estimated to affect more than 30 million people in the United States, features a failure of insulin signaling to reduce blood glucose levels. Since the 1990s researchers have recognized that insulin signaling is also an important regulator of longevity. For example, mutations in the gene that encodes the C. elegans insulin receptor DAF-2 can more than double the worm's lifespan. Gill and his colleagues focused on a variant form of the C. elegans receptor known as DAF-2B. It's a truncated version that contains the usual binding site for insulin, but doesn't respond as the normal version would by sending a cellular signal to initiate insulin production.

Although the discovery of this mechanism for regulating insulin signaling is a significant basic-science advance, it also suggests a new way of thinking about diabetes and even aging. The precise causes of the insulin resistance that underlies diabetes and is also seen to some extent with normal aging have never been fully illuminated. If humans also have a decoy insulin receptor like DAF-2B, then reversing its dysregulation in people who have insulin resistance might be a new strategy for better metabolic health.

"An alternatively spliced, non-signaling insulin receptor modulates insulin sensitivity via insulin peptide sequestration in C. elegans" *was written by Bryan Martinez, Pedro Reis Rodrigues, Ricardo Nuñez-Medina, Prosenjit Mondal, Neale Harrison, Museer Lone, Amanda Webster, Aditi U. Gurkar, Brock*

*Grill, and Matthew Gill, all of Scripps Research at the time of the study. Funding was provided by the National Institutes of Health.*

**Mysterious 'mutational freedom' in mitochondrial molecule may have been a key adaptation in animal evolution**

*Mitochondrial transfer-RNAs evolved special mutation-resilient structure in complex animals.*

A set of molecules needed for efficient energy production in cells apparently underwent a radical change during early animal evolution so they could continue to function despite their relatively high mutation rate, according to a new study from scientists at Scripps Research. In the study, published in *Nature Communications* in February 2020, the scientists analyzed a set of 22 closely related mitochondrial molecules. Mitochondria are tiny, bacteria-like "organelles" that are the major producers of chemical energy in cells; they contain their own small DNA genomes, which are separate from the main genome in the cell nucleus. The 22 mitochondrial molecules, called mitochondrial transfer RNAs (mt-tRNAs), play a central role in translating the information in mitochondrial genes into mitochondrial proteins.

The researchers found evidence that as more complex animals evolved from the simplest ones, their mt-tRNAs evolved to have an unusual basic structure, which conferred a remarkable capacity to keep working properly despite frequent mutations to their genes. Mitochondrial DNA is more vulnerable to mutations, especially in complex animals.

> "The mutational freedom of these novel mt-tRNA structures appears to be a powerful adaptive mechanism for withstanding the enhanced mutation rate of mitochondrial DNA in higher animals," says senior author Paul Schimmel, PhD, a professor in the Department of Molecular Medicine at Scripps Research.

Mitochondria are found—in numbers up to thousands per cell—in virtually all plants and animals, as well as in many simpler organisms. They're widely believed to have originated as bacteria that could live symbiotically inside the cells of some early, simple life forms. But after hundreds of millions of years of evolution, they have become essential producers of chemical energy in *all* complex species. They use oxygen to produce this energy—and that need for oxygen is why animals breathe. One of the problems with mitochondria, from a human health perspective, is that they are especially vulnerable to damage. Since mutations that occur randomly are much more likely to be harmful than helpful, genomes that are passed along in this manner could simply accumulate defects, from one generation to the next, until they become totally dysfunctional. Biologists still do not fully understand how mitochondria have avoided this fate.

In their study, Schimmel and colleagues, including co-corresponding author Bernhard Kuhle, PhD, a postdoctoral research associate in the Scripps Research Laboratories for tRNA Synthetase Research, addressed this question with an analysis of mitochondrial tRNAs. The 22 distinct mt-tRNAs account for most of the molecules encoded by the mitochondrial genome. Like non-mitochondrial tRNAs, these molecules work as essential "decoders" of the genetic code, linking nucleotide sequences copied out from genes to corresponding amino acids, which are the building blocks of proteins.

*Authors of "Relaxed sequence constraints favor mutational freedom in idiosyncratic metazoan mitochondrial tRNAs" are Bernhard Kuhle and Paul Schimmel of Scripps Research, and Joseph Chihade of Carleton College. Support was provided by the National Institutes of Health, the National Foundation for Cancer Research and the Skaggs Foundation.*

**Brain immune cell defect may help explain social impairments in males with autism**

*Immune cell mutations lead to inadequate pruning of brain connections in young male mice.*

Many cases of autism spectrum disorders (ASDs) may result from problems in immune cells that normally work to trim back unneeded brain connections in early life, suggests a new study led by scientists at Scripps Research. The study, published April 14, 2020 in Nature Communications, examined the effects of a set of gene mutations that account for a small percentage of autism disorders. These mutations are known to cause a general overproduction of many proteins in brain cells, but how that overproduction leads to autism behaviors has been a mystery. The scientists found evidence that the most relevant effect of this protein overproduction occurs in brain-based immune cells called microglial cells. These cells normally prune unneeded brain connections, or synapses, as the brain develops in childhood. The finding dovetails with the long-standing observation that autism disorders are four to five times more prevalent in males than females. It is also consistent with recent evidence that in people with ASDs, the brain commonly has a higher number of synapses than normal.

> "Our study suggests that impairments in microglia play a key role in the development of autism behaviors, at least in some cases, and may help explain the higher prevalence of autism disorders in males," says study senior author Baoji Xu, PhD, professor in the Department of Neuroscience at Scripps Research. "That, in turn, suggests that microglia might be a good target for future drugs that prevent or treat autism spectrum disorders."

Autism disorders are found in an estimated 2.4 percent of boys and 0.5 percent of girls. They involve a variety of abnormalities including social skill deficits, repetitive behaviors, and hypersensitivities to sounds and light. Research suggests that these disorders are largely genetic but can be caused by abnormalities in a variety of different genes acting alone or in combination. To date, well over 100 gene mutations and variants have been linked to ASDs. The researchers now are following up with studies to discover precisely why protein increases affect microglia in males so much more than in females. That discovery could prove to be an important piece of the puzzle of sex differences in autism—and could suggest new targets for autism treatments.

*The study, "*Elevated protein synthesis in microglia causes autism-like synaptic and behavioral aberrations*," was authored by Zhi-Xiang Xu, Ji-Wei Tan, Anna Riso, Ethan Xu, Guey-Ying Liao, Haifei Xu, Amy Clipperton-Allen, Damon Page and Baoji Xu, of Scripps Research; Gyu Hyun Kim, Sang-Hoon Lee, Na-Young Do, Chan Hee Lee and Kea Joo Lee of the Korea Brain Research Institute; Ye Sun of Florida Atlantic University; and Soonwook Kwon of Catholic University of Daegu. Funding was provided by the National Institutes of Health and the Ministry of Science and ICT of the Republic of Korea. Z.X.X. and H.X. were partially supported by a Training Grant in Alzheimer's Drug Discovery from the Lottie French Lewis Fund of the Community Foundation for Palm Beach and Martin Counties.*

**Treating cancer drug resistance may come at a cost to immune system, study suggests**

Sooner or later, most cancer patients develop resistance to the very chemotherapy drugs designed to kill their cancer, forcing oncologists to seek alternatives. Even more problematic, once a patient's tumor is resistant to one type of chemotherapy, it is much more likely to be resistant to other chemotherapies as well, a conundrum long known as multidrug resistance. Once patients reach this point, the prognosis is often grim, and for the last 35 years scientists have attempted to understand and block multidrug resistance in cancer by using experimental medicines.

A new study from scientists at Scripps Research in Florida raises red flags about this strategy. Inhibiting the key gene involved in cancer drug resistance has unintended side effects on specialized immune system cells called CD8+ cytotoxic T lymphocytes (CTLs), the team found. This could dull anti-cancer immune responses, and potentially increase vulnerability to infection, since CTLs are "killer" T cells,

essential in the fight against both viral and bacterial infections and tumors, says lead author Mark Sundrud, PhD, associate professor of Immunology and Microbiology at Scripps Research. Several genes are now recognized for contributing to multidrug resistance in cancer, but the first and most prominent of these is called multidrug resistance-1 (MDR1). Its discovery more than three decades ago set off a race to develop drugs that would inhibit expression of MDR1. But those MDR1 inhibitor drugs have consistently disappointed in clinical trials. The reasons behind these failures have remained enigmatic.

In a new study published April 2020 in the *Journal of Experimental Medicine*, Sundrud and colleagues including Scripps Research immunologist Matthew Pipkin, PhD, suggest that the repeated failure of MDR1 inhibitors in human cancer trials may be due to a previously unrecognized—and essential—function of the MDR1 gene in CD8+ cytotoxic T lymphocytes. Using new genetic approaches to visualize and functionally assess MDR1 expression in mouse cells, the team found that CTLs were unique in their constant and high-level expression of MDR1. In addition, preventing MDR1 expression in CTLs, or blocking its function using inhibitors previously tested in human cancer trials, sets off a chain reaction of CTL dysfunction, ultimately disabling these cells from fighting off viral or bacterial infections. Considering that these cells are also necessary for warding off most cancerous tumors, blocking MDR1 with existing inhibitors could also cripple natural immune responses to cancers, Sundrud says.

> "With the help of our collaborators at New York University Medical Center, we looked at mouse immune cells from five major lymphoid and nonlymphoid tissues: bone marrow, thymus, spleen, lung, and small intestine," Sundrud says. "It became clear that the types of cells that are key to fighting infections and cancers, are among those most sensitive to blocking MDR1 function."

The team is now looking to use this new knowledge to finally nail down a unifying function of MDR1 in all cells, whether it is in CTLs responding to infections, or cancer cells trying to deal with chemotherapeutic agents. In the shorter term, Sundrud and colleagues plan to explore new approaches to re-design existing MDR1 inhibitors to specifically target only cancer cells.

*Additional authors of "Physiological expression and function of the MDR1 transporter in cytotoxic T lymphocytes," are co-author Sergei B. Koralov of New York University Medical Center; first authors Mei Lan Chen of Scripps Research and Amy Sun of New York University Medical Center; as well as Wei Cao, Amber Eliason, Kayla M. Mendez, Adam J. Getzler, Shanel Tsuda, Huitian Diao, Clever Mukori, Nelson E. Bruno, Sang Yong Kim, and Matthew E. Pipkin all of Scripps Research.*

*Support for the study came from the State of Florida, the National Institutes of Health and the Crohn's and Colitis Foundation Senior Research Award to Sundrud A. Sun received NIH medical scientist training grants.*

**Parkinson's dyskinesia mechanism explained**

*Involuntary movements caused by dopamine replacement therapy can be alleviated through suppression of RasGRP1, study finds.*

Many people with Parkinson's disease eventually develop debilitating movements called dyskinesia, a side effect of their much-needed dopamine replacement medication. The mechanism underlying this unwanted side effect has been unknown, until now. An international collaboration led by Scripps Research, Florida has found a key cause, and with it, potentially, a new route to providing relief.

Dopamine replacement therapy makes Parkinson's symptoms much better at first, but eventually treatment gives way to uncontrollable, jerky body movements. But why? New research shows that underlying this development is the therapy's unintended boost of a protein with the unwieldy name Ras-guanine nucleotide-releasing factor 1, or RasGRP1 for short. This boost in RasGRP1 produces a cascade

of effects which lead to abnormal, involuntary movements known as LID, or L-DOPA-induced dyskinesia, says co-lead author Srinivasa Subramaniam, PhD, associate professor of neuroscience at Scripps Research, Florida. Encouragingly, the collaboration found that in dopamine-depleted mice and other animal models, inhibiting production of RasGRP1 in the brain during dopamine replacement diminished the involuntary movements without negating the useful effects of the dopamine therapy.

Taken together, the research offers a new path to easing Parkinson's dyskinesia while allowing maintenance of dopamine replacement therapy, Subramaniam says. Subramaniam's group has long been interested in cellular signaling in the brain underlying motor movements, and how it is affected by brain diseases, including Huntington's and Parkinson's.

> "Parkinson's patients describe treatment-induced dyskinesia as one of the most debilitating features of their illness," Subramaniam says. "These studies show that if we can down-regulate RasGRP1 signaling before dopamine replacement, we have an opportunity to greatly improve their quality of life."

The study, "RasGRP1 is a causal factor in the development of L-DOPA-induced dyskinesia in Parkinson's disease," was published in the journal *Science Advances* May 1, 2020. In addition to Subramaniam, the co-lead author is Alessandro Usiello, PhD, of the University of Campania Luigi Vanvitelli, Caserta, Italy, and the Behavioural Neuroscience Laboratory at Ceinge Biotecnologie Avanzate, Naples, Italy.

Dopamine is a neurotransmitter and hormone that plays a key role in movement, learning, memory, motivation, and emotion. Parkinson's develops when dopamine-producing neurons in a region of the mid-brain called the substantia nigra stop working or die. It's a brain region associated with both movement initiation and reward, so its impairment causes a wide variety of symptoms, including stiffness, balance problems, walking difficulty, tremor, depression and memory issues.

Doctors treat Parkinson's with dopamine replacement therapy, often a medicine called levodopa. The brain converts levodopa into dopamine, and at proper doses, this leads to resolution of symptoms. But as dose and duration grow, a side effect called dyskinesia can develop. After a decade, about 95 percent of Parkinson's patients will experience some degree of involuntary dyskinesia, Subramaniam says.

Dyskinesia is different than tremor, according to the Michael J. Fox Foundation.

The next steps in the research will be discovering the best route to selectively reducing expression of RasGRP1 in the striatum while not affecting its expression in other areas of the body, Subramaniam says. "It's rare for a nonprofit institution to possess the medicinal chemistry and drug development expertise needed to identify and develop such a therapy, but we have that at Scripps Research," Subramaniam says. "Our next task is to develop suitable compounds capable of blocking RasGRP1 in the striatum."

*In addition to Subramaniam and Usiello, the authors of* the study *are co-first authors Mehdi Eshraghi, Uri Nimrod Ramírez-Jarquín and Neelam Shahani; Supriya Swarnkar, Nicole Galli, Oscar Rivera, George Tsaprailis, Catherina Scharager-Tapia and Gogce Crynen, all of Scripps Research, Florida; co-authors Tommaso Nuzzo and Arianna De Rosa of the University of Campania Luigi Vanvitelli, Caserta, Italy, and the Behavioural Neuroscience Laboratory at Ceinge Biotecnologie Avanzate, Naples; Qin Li and Erwan Bezard of Motac Neuroscience in Manchester, United Kingdom and the China Academy of Medical Sciences in Beijing, China; and Marie-Laure Thiolat of the Institut des Maladies Neurodegeneratives and the Universite de Bordeaux, Institute des Maladies Neurodegeneratives of Bordeaux, France. This work was supported by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health, the Cure for Huntington Disease Initiative Foundation, the Fondazione Cariplo and Ricerca Ateneo, Universita Campania.*

**Cancer cells' growth amid crowding reveals nuanced role for known oncogene**

*Cell-to-cell contact should stall proliferation, but cancer misses the message.*

Like subway commuters on a crowded train, cells generally prefer not to be packed in too tightly. In fact, they have set up mechanisms to avoid this, a phenomenon called "contact inhibition." A hallmark of cancer cells is that they lack this contact inhibition, and instead become pushy, facilitating their spread. Scientific understanding of the mechanism underlying this cell behavior change has had many gaps. A new paper from the lab of Joseph Kissil, PhD, professor of Molecular Medicine at Scripps Research in Florida, provides important new insights. Writing in *Cancer Research*, a journal of the American Association for Cancer Research in May 2020, Kissil and colleagues offer new details about how the "stop-growth" signal unfurls during cell-to-cell contact, and how disruption of that "stop-growth" signal can promote cancer. A key player is a protein called YAP, a regulator of gene expression. YAP is a major effector of a pathway referred to as the Hippo pathway, so named after geneticists discovered that mutations to the HPO gene produced lumpy, hippo-like tissue overgrowth in fruit fly models. Healthy cells and developing organs "know" when they should grow and when they should stop growing, based on multiple signaling molecules. These signals are transmitted by YAP and the Hippo pathway. Tracing out those signals is not only central to understanding our basic biology, but to finding new ways to attack cancers with precision therapies, Kissil explains.

> "What we show here is that YAP can also turn off genes, not just turn them on," Kissil says. "It shuts down genes that would otherwise prevent cells from proliferating."

In the end, like a broken down subway line, disruption of the Hippo pathway at any point can redirect the cell's behavior, away from contact inhibition. The discovery of YAP's dual role as both promotor and repressor of gene transcription provides important information in the efforts to make cancer drugs that act on YAP. Finding the players that both interact with YAP and have a functional role in promoting cancer growth required use of a genome-wide bioinformatics technique called ChIP-seq. The work involved collaboration with the labs of Matthew Pipkin, PhD, of Scripps Research in Florida, and Michael Kareta, PhD, of Sanford Research in Sioux Falls, South Dakota. The team looked at YAP in the context of cell crowding. They learned that YAP's role involves recruitment of other interacting proteins that include YY1, also known as Yin-Yang 1, EZH2 and a protein complex called PRC2. Those will also be important to study further, Kissel says, as well as the interaction of these players in the context of cancer drug resistance.

*The study,"*YAP-mediated Recruitment of Q2 YY1 and EZH2 Represses Transcription of Key Cell-Cycle Regulators*," was published online in the journal* Cancer Research *on Thursday, May 14, 2020. In addition to Kissil, Pipkin and Kareta, authors are Sany Hoxha, Alyssa Shepard, Scott Troutman, Huitian Diao, Joanne Doherty, Michalina Janiszewska, Robert Witwicki, and William Ja, all of Scripps Research, Florida. Funding for the research was provided by the National Institutes of Health and by generous donations from the Frenchman's Creek Women for Cancer Research.*

**Solving the 175-year-old medical mystery of anesthesia's effects**

*Billiard-like break shot to cell-membrane structures triggers brain's loss of consciousness from anesthesia, scientists find.*

Surgery would be inconceivable without general anesthesia, so it may come as a surprise that despite its 175-year history of medical use, doctors and scientists have been unable to explain how anesthetics temporarily render patients unconscious. A new study from Scripps Research published in May 2020 in the Proceedings of the National Academies of Sciences (PNAS) solves this longstanding medical mystery. Using modern nanoscale microscopic techniques, plus clever experiments in living cells and fruit flies, the scientists show how clusters of lipids in the cell membrane serve as a missing go-between

in a two-part mechanism. Temporary exposure to anesthesia causes the lipid clusters to move from an ordered state, to a disordered one, and then back again, leading to a multitude of subsequent effects that ultimately cause changes in consciousness. The discovery by chemist Richard Lerner, MD, and molecular biologist Scott Hansen, PhD, settles a century-old scientific debate, one that still simmers today: Do anesthetics act directly on cell-membrane gates called ion channels, or do they somehow act on the membrane to signal cell changes in a new and unexpected way? It has taken nearly five years of experiments, calls, debates and challenges to arrive at the conclusion that it's a two-step process that begins in the membrane, the duo say. The anesthetics perturb ordered lipid clusters within the cell membrane known as "lipid rafts" to initiate the signal.

> "We think there is little doubt that this novel pathway is being used for other brain functions beyond consciousness, enabling us to now chip away at additional mysteries of the brain," Lerner says.

Lerner, a member of the National Academy of Sciences, is a former president of Scripps Research, and the founder of Scripps Research's Jupiter, Florida campus. Hansen is an associate professor, in his first posting, at that same campus.

**The Ether Dome** Ether's ability to induce loss of consciousness was first demonstrated on a tumor patient at Massachusetts General Hospital in Boston in 1846, within a surgical theater that later became known as "the Ether Dome." So consequential was the procedure that it was captured in a famous painting, "First Operation Under Ether," by Robert C. Hinckley. By 1899, German pharmacologist Hans Horst Meyer, and then in 1901 British biologist Charles Ernest Overton, sagely concluded that lipid solubility dictated the potency of such anesthetics. Hansen recalls turning to a Google search while drafting a grant submission to investigate further that historic question, thinking he couldn't be the only one convinced of membrane lipid rafts' role. To Hansen's delight, he found a figure from Lerner's 1997 PNAS paper, "A hypothesis about the endogenous analogue of general anesthesia," that proposed just such a mechanism. Hansen had long looked up to Lerner—literally. As a predoctoral student in San Diego, Hansen says he worked in a basement lab with a window that looked directly out at Lerner's parking space at Scripps Research.

> "I contacted him, and I said, 'You are never going to believe this. Your 1997 figure was intuitively describing what I am seeing in our data right now,'" Hansen recalls. "It was brilliant."

For Lerner, it was an exciting moment as well. "This is the granddaddy of medical mysteries," Lerner says. "When I was in medical school at Stanford, this was the one problem I wanted to solve. Anesthesia was of such practical importance I couldn't believe we didn't know how all of these anesthetics could cause people to lose consciousness."

Many other scientists, through a century of experimentation, had sought the same answers, but they lacked several key elements, Hansen says: First, microscopes able to visualize biological complexes smaller than the diffraction limits of light, and second, recent insights about the nature of cell membranes, and the complex organization and function of the rich variety of lipid complexes that comprise them.

**From order to disorder** Using Nobel Prize-winning microscopic technology, specifically a microscope called dSTORM, short for "direct stochastical optical reconstruction microscopy," a post-doctoral researcher in the Hansen lab bathed cells in chloroform and watched something like the opening break shot of a game of billiards. Exposing the cells to chloroform strongly increased the diameter and area of cell membrane lipid clusters called GM1, Hansen explains. What he was looking at was a shift in the GM1 cluster's organization, a shift from a tightly packed ball to a disrupted mess, Hansen says. As it grew disordered, GM1 spilled its contents, among them, an enzyme called phospholipase D2 (PLD2).

Tagging PLD2 with a fluorescent chemical, Hansen was able to watch via the dSTORM microscope as PLD2 moved like a billiard ball away from its GM1 home and over to a different, less-preferred lipid cluster called PIP2. This activated key molecules within PIP2 clusters, among them, TREK1 potassium ion channels and their lipid activator, phosphatidic acid (PA). The activation of TREK1 basically freezes neurons' ability to fire, and thus leads to loss of consciousness, Hansen says. Lerner insisted they validate the findings in a living animal model. The common fruit fly, *drosophila melanogaster*, provided that data. Deleting PLD expression in the flies rendered them resistant to the effects of sedation. In fact, they required double the exposure to the anesthetic to demonstrate the same response.

Hansen and Lerner say the discoveries raise a host of tantalizing new possibilities that may explain other mysteries of the brain, including the molecular events that lead us to fall asleep. Lerner's original 1997 hypothesis of the role of "lipid matrices" in signaling arose from his inquiries into the biochemistry of sleep, and his discovery of a soporific lipid he called oleamide. Hansen and Lerner's collaboration in this arena continues.

*The paper, "*Studies on the mechanism of general anesthesia,*" appears May 29, 2020, in PNAS. In addition to Lerner and Hansen, the authors are Mahmud Arif Pavel, E. Nicholas Petersen and Hao Wang, all of Scripps Research. The work was supported by a Director's New Innovator Award from the National Institutes of Health, and a JPB Foundation Grant. The Joseph B. Scheller and Rita P. Scheller Charitable Foundation have generously provided Petersen's graduate fellowship.*

**Mutated coronavirus shows significant boost in infectivity**

*COVID-19-causing viral variant taking over in the United States and Europe now carries more functional, cell-binding spikes.*

A tiny genetic mutation in the SARS coronavirus 2 variant circulating throughout Europe and the United States significantly increases the virus' ability to infect cells, lab experiments performed at Scripps Research show.

> "Viruses with this mutation were much more infectious than those without the mutation in the cell culture system we used," says Scripps Research virologist Hyeryun Choe, PhD, senior author of the study. The mutation had the effect of markedly increasing the number of functional spikes on the viral surface, she adds. Those spikes are what allow the virus to bind to and infect cells. "The number—or density—of functional spikes on the virus is 4 or 5 times greater due to this mutation," Choe says.

The spikes give the coronavirus its crown-like appearance and enable it to latch onto target cell receptors called ACE2. The mutation, called D614G, provides greater flexibility to the spike's "backbone," explains co-author Michael Farzan, PhD, co-chairman of the Scripps Research Department of Immunology and Microbiology. More flexible spikes allow newly made viral particles to navigate the journey from producer cell to target cell fully intact, with less tendency to fall apart prematurely, he explains. There has been much debate about why COVID-19 outbreaks in Italy and New York have so quickly overwhelmed health systems, while early outbreaks in places like San Francisco and Washington state proved more readily managed, at least initially. Was it something about those communities and their response, or had the virus somehow changed? All viruses acquire minute genetic changes as they reproduce and spread. Those changes rarely impact fitness or ability to compete. The SARS-CoV-2 variant that circulated in the earliest regional outbreaks lacked the D614G mutation now dominating in much of the world.

But was that because of the so-called "founder effect," seen when a small number of variants fan out into a wide population, by chance? Choe and Farzan believe their biochemical experiments settle the question.

Now undergoing peer review, Choe and Farzan's experiments were released in June 2020 at bioRxiv, amid news reports of its findings. Choe and Farzan have studied coronaviruses for nearly 20 years, since the first outbreak of SARS, a similar virus. They were the first to discover in 2003 that SARS bound to the ACE2 receptor on cells. Others' experiments have shown the SARS-CoV-2 virus binds the same ACE2 receptor. But Farzan and Choe note a key structural difference between spike proteins on the first SARS virus and this new pandemic strain. With both, under an electron microscope, the spike has tripod shape, with its three segments bound together at a backbone-like scaffold. But SARS-CoV-2 is different. Its tripod is divided in two discreet segments, S1 and S2. It is still unknown whether this small mutation affects the severity of symptoms of infected people, or increases mortality, the scientists say. While ICU data from New York and elsewhere reports a preponderance of the new D614G variant, much more data, ideally under controlled studies, are needed, Choe says.

*In addition to senior authors Choe and Farzan, the authors include first authors Lizhou Zhang, Cody Jackson and Huihui Mou, plus co-authors Amrita Ojha, Erumbi Rangarajan and Tina Izard, all of Scripps Research. The work was supported by the National Institutes of Health through an administrative supplement for coronavirus research.*

**Huntington's disease progression involves DNA damage sensor**

*Abnormal cellular housekeeping and inflammation point to potential target for treating fatal neurodegenerative disorder.*

Families afflicted by Huntington's disease face anguishing challenges. An incurable genetic disease, Huntington's symptoms usually appear after age 30, meaning parents often pass the mutant Huntington's gene to their children—even grandchildren—before they discover they are carriers. Striking in the prime of life, it damages movement control, mood stability and thinking before ultimately causing death. At least 30,000 people in the United States live with the diagnosis.

> "So far there has been no effective therapy available for the disease because we haven't yet understood the molecular mechanism, even though we know the faulty gene," says neuroscientist Srinivasa Subramaniam, PhD, associate professor at Scripps Research in Florida, who has been doing Huntington's research for 15 years.

A new study from Subramaniam and his team provides new insights into the molecular events that lead to the progressive destruction of brain cells in Huntington's. The research reveals a central role for a damage-sensing enzyme called cGAS that seems to ignite a cascade of inflammation and excessive cellular housekeeping, a process called autophagy. Their study, appeared in June 2020 in the *Proceedings of the National Academy of Sciences*, raises the possibility that reducing cGAS activity in the brain may be a treatment strategy worth testing in further studies, Subramaniam says. Subramaniam and his colleagues discovered that the cGAS enzyme is produced at abnormally high levels in Huntington's-mutant neurons from the striatum, the brain region that is hit earliest and hardest by Huntington's disease. The team also found that the high levels of cGAS in striatal Huntington's neurons drives inflammatory processes in these cells as well as a related cellular waste-removal process called autophagy. Both inflammation and autophagy were known to occur excessively or otherwise abnormally in Huntington's and have been suspected of contributing to the neuronal destruction that underlies the disease.

*"Cyclic GMP-AMP Synthase Promotes the Inflammatory and Autophagy Responses in Huntington Disease," was written by Manish Sharma, Sumitha Rajendra Rao, Neelam Shahani, Uri Nimrod Ramirez Jarquin, and Srinivasa Subramaniam, all of Scripps Research at the time of the study.*

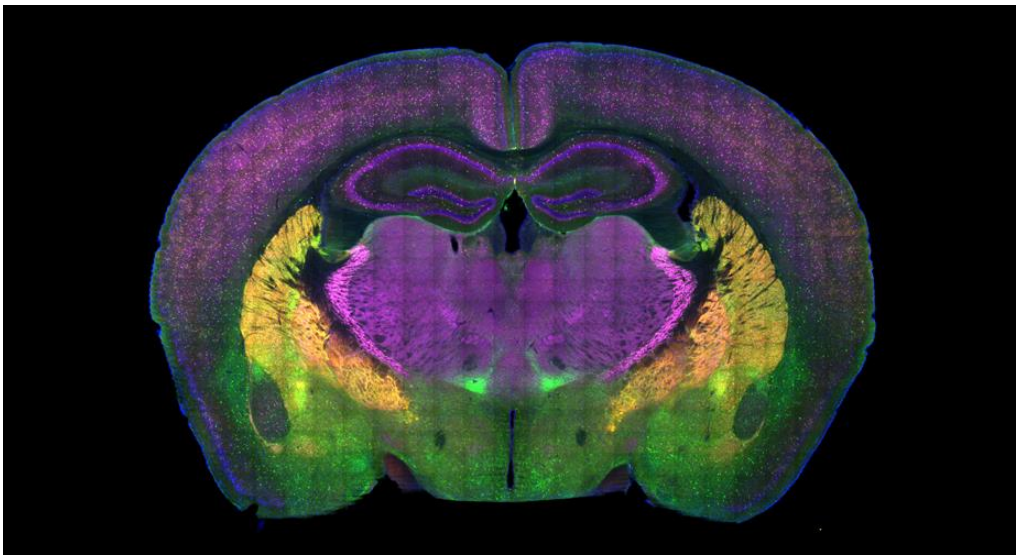
*Funding was provided by the National Institute of Neurological Disorders and Stroke, the Cure Huntington Disease Initiative, and the Community Foundation for Palm Beach and Martin Counties.*

**Autism researchers map brain circuitry of social preference**

*Discovery empowers research into needed therapies, scientists say.*

Some individuals love meeting new people, while others abhor the idea. For individuals with conditions such as autism, unfamiliar social interactions can produce negative emotions such as fear and anxiety. A new study from Scripps Research reveals how two key neural circuits dictate the choice between social approach and avoidance. Neuroscientists who study autism have sought to define the brain circuits underlying these challenges, to enable more precise diagnosis, and to develop protocols for testing the effectiveness of therapeutic interventions. Brain mapping efforts have implicated multiple areas, including the emotional center of the brain and the region responsible for coordinating thoughts and actions. Assigning cause and effect to changes in these regions to the symptoms of autism, however, has been challenging.

The study from the lab of neuroscientist Damon Page, PhD, uses a variety of innovative techniques to address this challenge, finding two specific circuits capable of independently controlling social preference in mice. Both link the areas of higher-level thought and decision-making in the prefrontal cortex to the emotional regulation center of the brain, the amygdala. Sociable animals like mice – and humans – generally seek out social engagement, which produces benefits including increased resilience to stress, Page explains. But in conditions such as autism, schizophrenia and others that feature social impairments, an unexpected social encounter may produce a negative emotional reaction. Difficulty communicating and interacting with others is a hallmark of autism spectrum disorders, which now affect 1 in 34 U.S. boys and 1 in 54 girls age 8, according to the National Institutes of Mental Health.



*A cross-section of a mouse brain reveals some of the regions involved in the choice between social approach and avoidance.*
*Credit: Page lab, Scripps Research, Florida. (Red is a genetic reporter for GABAergic neurons, green and magenta are immunohistochemical markers for subsets of GABAergic neurons, and blue is DAPI, a nucleic acid stain.*

"To understand something properly, you need to know where to look. It's a needle-in-the-haystack problem," Page says. "Understanding how this circuit works normally enables us to now ask the questions, 'How is this wiring changed in a condition like autism? How do therapeutic interventions impact the function of this circuit?'"

The group found that one neural circuit connecting the mouse infralimbic cortex to the basolateral amygdala impairs social behavior if its activity is dialed down. The other key circuit connects the prelimbic cortex to the basolateral amygdala. Dialing up activity of that circuit produced similarly impaired social behavior, says Aya Zucca, the study's co-first author. Zucca notes that both mice and

humans use corresponding brain regions to process social information, so the mouse model is a good one for studying these issues.

*The study, "Social Behavior Is Modulated by Valence-Encoding mPFC-Amygdala Sub-circuitry," appeared in the journal Cell Reports in July 2020. In addition to Page and Zucca, contributors include co-first author Wen-Chin Huang, currently at the Massachusetts Institute of Technology's Picower Institute for Learning and Memory, and Jenna Levy, of Scripps Research. This research was supported by the National Institutes of Health grant, Ms. Nancy Lurie Marks, the Fraternal Order of Eagles, the American Honda and Children's Healthcare Charity, and an anonymous donor.*

**Chemists synthesize natural anti-cancer compound with efficient new process**

*Collaborating labs at Scripps Research developed a way to seamlessly create the compound's complex structure.*

Scripps Research chemists Hans Renata, PhD, and Alexander Adibekian, PhD, have discovered a way to efficiently create a synthetic version of a valuable natural compound called cepafungin I, which has shown promise as an anti-cancer agent. Through this, they were able to understand how the bacterial secretion is able to block a piece of molecular machinery known as a proteasome—a strategy that many existing cancer medications use to destroy tumor cells. They found that cepafungin I bound to not one but two places on the proteasome, enacting a powerful result. Their report appeared in the journal *Cell Chemical Biology* in July 2020.

> "Because cepafungin I is able to engage the proteasome in two ways, it allows for amplification of its effect," Renata says. "We showed that this compound elicits many similar downstream biological responses as the FDA-approved chemotherapy bortezomib, while also having certain qualities that may translate into fewer unwanted side effects for patients."

Cepafungin I first intrigued researchers because of its usefulness as an antifungal substance, and later as a promising anti-cancer agent. It kills cells by acting on the proteasome, which is responsible for clearing away the "garbage" produced by cells. When the proteasome's function is blocked, cells are overcome with their waste and die. But making enough of the compound to be able to study its activity or enable its eventual use a medication has proven challenging, due largely to its complex molecular structure. In the field of chemistry, scientists seek to create the desired structure in as few steps as possible, which leads to cost and time savings. But with complex compounds, that isn't an easy task. The Scripps Research team was able to overcome these challenges and synthesize the compound in just nine steps. For comparison, a related compound known as glidobactin A was synthesized in 21 steps in 1992—and that was considered a landmark at the time.

After creating the compound, the chemists discovered that in addition to being exceptionally selective at targeting two sites on the proteasome, it didn't show any undesired cross-reaction with other proteins in cells, a feature that could make it a better drug candidate. Three proteasome inhibitors—bortezomib, carfilzomib and ixazomib—have already been approved by the U.S. Food and Drug Administration for the treatment of multiple myeloma. Graduate student Anton Shuster, also an author of the new research, noted that the team's discoveries were made possible by a close collaboration of labs with different expertise. Going forward, the scientists plan to continue structure-guided design of similar molecules with alternative structural features in search of useful compounds with superior anti-cancer activity.

*Authors of the study, "Concise Chemoenzymatic Total Synthesis and Identification of Cellular Targets of Cepafungin I," are Renata, Adibekian, Amatuni and Shuster, all of Scripps Research.*

**Chemists hijack bacterial enzymes to create complex molecules normally made by plants**

*In their synthesis of molecules known as "oxidized diterpenes," scientists demonstrate a strategy for harnessing enzymes more broadly to build new medicines.*

Chemists at Scripps Research have efficiently created three families of complex, oxygen-containing molecules that are normally obtainable only from plants. These molecules, called terpenes, are potential starting points for new drugs and other high-value products—marking an important development for multiple industries. In addition, the new approach could allow chemists to build many other classes of compounds. The chemistry feat is detailed in the Aug. 13 edition of the journal *Science*.

The key to this new method of making molecules is the harnessing, or hijacking, of natural enzymes—from bacteria, in this case—to assist in complex chemical transformations that have been impractical or impossible with synthetic chemistry techniques alone, says principal investigator Hans Renata, PhD, an assistant professor in the Department of Chemistry at Scripps Research. Natural enzymes that help build molecules in cells usually perform only one or two highly specific tasks. But the Scripps Research team showed that natural enzymes, even without modification, can be made to perform a wider range of tasks.

> "We think that in general, enzymes are a mostly untapped resource for solving problems in chemical synthesis," Renata says. "Enzymes tend to have some degree of promiscuous activity, in terms of their ability to spur chemical reactions beyond their primary task, and we were able to take advantage of that here."

Enzymes, among other functions, help build molecules in all plant, animal and microbial species. Inspired by their efficiency in constructing highly complex molecules, chemists for more than half a century have used enzymes in the lab to help build valuable compounds, including drug compounds—but usually these compounds are the same molecules the enzymes help build in nature. Harnessing natural enzymes in a broader way, according to their basic biochemical activity, is a new strategy with vast potential.

The synthesis of each compound, in less than 10 steps for each, was a hybrid process combining current organic synthesis methods with enzyme-mediated synthesis starting from an inexpensive compound called stevioside, the main component of the artificial sweetener Stevia. The chief hurdle was the direct replacement of hydrogen atoms with oxygen atoms in a complex pattern on the carbon-atom skeleton of the starting compound. Current organic synthesis methods have a limited arsenal for such transformations. However, nature has produced many enzymes that can enable these transformations—each capable of performing its function with a degree of control unmatched by man-made methods.

The three enzymes used, which were identified and characterized by Shen, Renata and colleagues only last year, are produced naturally by a bacterium—one of the 200,000-plus species in the Microbial Strain Collection at Scripps Research's Natural Products Discovery Center. The chemists now intend to use their new approach to make useful quantities of the nine compounds, as well as chemical variants of the compounds, and, with collaborating laboratories, explore their properties as potential drugs or other products. Just as importantly, the researchers say, they are working to identify reactions and enzymes that will allow them to extend their approach to other classes of molecules. Central to all these efforts is the ongoing development of methods to sift through the DNA of microbes and other organisms to identify the enzymes they encode—and predict the activities of those enzymes. Billions of distinct enzymes exist in plants, animals, and bacteria on Earth and only a tiny fraction of them have been catalogued to date.

*Other co-authors of the study, "Divergent synthesis of complex diterpenes through a hybrid oxidative approach," were Liao-Bin Dong, Li-Cheng Yang, and Jeffrey Rudolf, all of Scripps Research at the time of the study. The research was funded by the National Institutes of Health.*

**Heart repair factor boosted by RNA-targeting compound**

*Disney lab collaboration reawakens heart cells' silenced VEGF-A healing system by targeting non-coding RNA in cellular models.*

A heart attack can leave parts of the heart permanently scarred and stiff, resulting in prolonged disability and potential progression toward heart failure. Scientists have studied various ways to repair or regenerate such damaged heart tissue, with limited success. A new study from Scripps Research Chemist Matthew Disney, PhD, shows that by targeting an essential biomolecule that surges in failing heart muscle, it may be possible to one day heal damaged heart tissue with medication. In a study published August 2020 in the journal *Nature Chemistry*, the Disney collaboration describes the discovery of the first compounds able to restart cellular production of a factor called VEGF-A, short for vascular endothelial growth factor A, in cellular models. Research over many years has shown VEGF-A acts as a signal to stem cells, causing them to rebuild blood vessels and muscle in damaged heart tissue, and improve blood flow. Targeting RNAs, the "middleman" between genes and protein production, makes logical sense, but doing so with medicines was once deemed unfeasible. RNAs were long thought to be poor small-molecule drug targets due to their simple four-base makeup and dynamic shape. Through the years, Disney and colleagues have developed an array of computational and chemical tools designed to overcome those barriers.

> "During a heart attack, the injury causes proteins that could promote new, healthy blood vessel growth to go silent," Disney explains. "We analyzed the entire pathway for how the protein is silenced, and then we used that information to identify how to reinvigorate its expression."

Lead author Hafeez Haniff, a graduate student at Scripps Research, Florida, analyzed the genomics underlying VEGF-A production to assess optimal RNA drug targets, working in collaboration with scientists at AstraZeneca. The team selected a microRNA precursor called pre-miR-377, finding it acts like a dimmer switch for VEGF-A production in failing heart muscle. They then used Disney's computational and chemical tools, in conjunction with a diverse set of compounds from AstraZeneca's collection, in search of chemical partners able to selectively bind to the key conserved structural features of pre-miR-377. Disney called their success a "test case" that shows it is possible to reliably and predictably develop medicinal compounds for pre-defined RNA targets and induce protein production in cellular models. Because of the largescale screening done to identify TGP-377, Disney says the group expanded by 20-fold the data set of known RNA-binding small molecules generally, with implications for multiple incurable diseases.

*Authors of the study, "Design of a small molecule that stimulates vascular endothelial growth factor A enabled by screening RNA fold–small molecule interactions," include Disney and Haniff, plus Xiaohui Liu, Daniel Abegg, Alexander Adibekian, Elizabeth Lekah, Gogce Crynen and Michael D. Cameron of Scripps Research, Florida; as well as Laurent Knerr, Malin Lemurell, and Jonas Boström, of AstraZeneca's Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D; and Ilyas Yildirim and Kye Won Wang of the Department of Chemistry and Biochemistry, Florida Atlantic University, Jupiter, Florida. This work was funded by the National Institutes of Health and AstraZeneca.*

**Wiring the eyes to the brain for color vision**

*Color-discriminating cone cells in the retina use a pair of "adhesion" proteins to connect to the brain.*

Cone cells in the retina, which are meant to work in daylight and enable color vision, normally use a specific set of proteins during development to connect to other nerve cells in the retina and the brain, according to a study led by neuroscientists at Scripps Research. The finding, reported September 2020 in the *Proceedings of the National Academy of Sciences*, solves the mystery of how cones form their

distinctive brain connections, giving humans and other animals their sophisticated and powerful vision sense. The basic neuroscience discovery may aid future efforts to boost vision lost due to retina degeneration, which is common in the elderly, and may potentially help connect lab-grown light-sensing prosthetics that cure blindness. Our eyes are equipped with two kinds of light sensors known as photoreceptors: the rods that we use for seeing under very dim lighting and cones that we use ubiquitously throughout the day to see things in color. Detecting the light, however, is only the first step for us to be able to see. Photoreceptors then need to be able to transmit their signals to the brain. They do so by establishing highly selective contacts with other neural cells in the retina that ultimately pass the information to the brain, much like plugging an electrical device into a socket.

The research team, led by principal investigator Kirill Martemyanov, PhD, professor and chair of the Department of Neuroscience at Scripps Research's Florida campus, discovered that a pair of cell adhesion molecules called ELFN1 and ELFN2 does the trick. Back in 2015, his team discovered that a protein called ELFN1 enables rod cells to hook up to nearby nerve cells in the retina. A rod cell is a long, slender cell with photosensitive molecules at one end for detecting light photons, and a stalk-like projection at the other end for sending their signals brainward. With the new discovery, he says, we finally know how two types of primary photoreceptor cells, which we rely on for all of our vision sense, are sending their information to the brain. And importantly, this fundamental knowledge may one day translate into novel treatments for vision loss.

*"Interplay between cell adhesion molecules governs synaptic wiring of cone photoreceptors" was authored by Yan Cao, Yuchen Wang, Henry Dunn, Cesare Orlandi and Kirill Martemyanov, of Scripps Research; Nicole Shultz, Naomi Kamasawa, and David Fitzpatrick, of Max Planck Florida Institute; Wei Li of the National Eye Institute; Christina Zeitz of Sorbonne Université; and William Hauswirth of the College of Medicine at the University of Florida at Gainesville. The study was funded by the National Institutes of Health, the French Muscular Dystrophy Association, Retina France and the Agence Nationale de la Recherche.*

**New gene implicated in neuron diseases**

*A defective protein quality control system leads to motor neuron death, as seen in disorders such as ALS.*

Failures in a quality control system that protects protein-building fidelity in cells can lead to motor neuron degeneration and related diseases, according to a new study from an international team co-directed by Scripps Research molecular biologist Claudio Joazeiro, PhD. Motor neurons control movement, breathing, swallowing and speaking. Their death is a hallmark of progressive diseases such as spinal muscular atrophy and ALS, also known as Lou Gehrig's disease. Understanding what can cause motor neurons to die is a key to developing precision treatments. Scientists are finding that the causes of motor neuron diseases are many. The study, appearing in the August 2020 edition of the journal *Nature Communications*, singles out several variants of a gene called NEMF as a new driver of motor neuron diseases. NEMF, short for "nuclear export mediator factor," is known for its role in helping clear glitches that inevitably occur during protein production by cellular organelles called ribosomes. The research was led by both Joazeiro, who has joint appointments at Scripps Research in Jupiter, Florida and the Center for Molecular Biology of Heidelberg University in Germany, and Gregory Cox, PhD, of the Jackson Laboratory of Mammalian Genetics in Bar Harbor, Maine.

A decade ago, Joazeiro discovered an enzyme, the E3 ubiquitin ligase listerin/Ltn1, that works in a specialized quality control process now known as RQC, or ribosome-associated quality control. He and his team also found that inactivation of the enzyme causes motor neuron degeneration in mice. However, whether neurodegeneration resulted from defective ribosome-associated quality control or

some other function of listerin, remained unclear. At the Jackson Laboratory, Cox had been studying mice with mutations in another quality control factor, NEMF. They exhibited movement difficulties including walking and gripping. The labs teamed up to investigate whether those defects resulted from a neurodegenerative process. They wanted to find the molecular mechanisms at work.

> "The results provide strong evidence that dysfunction of ribosomal quality control causes neurodegeneration," Joazeiro says.

Working through GeneMatcher, a tool for patients developed at the Baylor-Hopkins Center for Mendelian Genomics in Texas, the team identified nine patients from seven unrelated families who had likely pathogenic NEMF variants and displayed neuromuscular disease, along with a variety of developmental issues including speech delay and intellectual disability. The team is now investigating the role of ribosome-associated quality control in other related diseases, he adds. Another fascinating takeaway from this research is that this pathway of protein quality control appears to be necessary across species. Together with the findings that disabling the system results in neurodegeneration, this evolutionary conservation highlights the importance of aberrant protein disposal, and also suggests the system's development may have played a critical role enabling the evolution of complex organisms, Joazeiro says.

*In addition to lead co-authors Joazeiro and Cox, contributors to the study, "NEMF mutations that impair ribosome-associated quality control are associated with neuromuscular disease," include co-first authors Paige B. Martin of the Jackson Laboratory of Mammalian Genetics in Bar Harbor, Maine and the University of Maine, and Yu Kigoshi-Tansho of the Center for Molecular Biology of Heidelberg University. Additional authors are: Ryo Yonashiro and Tina Müller of Scripps Research, Florida; Jennifer Stauffer of the Jackson Laboratory of Mammalian Genetics; Rajesh Kumar of Heidelberg University; Roger Sher of Stony Brook University; Gianina Ravenscroft, Denise Howting and Nigel Laing of the University of Western Australia; Christopher Griffith of the University of South Florida College of Medicine; William Allen of the Mission Fullerton Genetics Center; Davut Pehlivan, Jennifer E. Posey and James Lupski of the Baylor College of Medicine; Tamar Haral of Hadassah-Hebrew University Medical Center; Martin Zenker and Denny Schanze of the Institute of Human Genetics, Otto-von-Guericke University, Magdeburg; Eissa A. Faqeih of the Department of Genetics, King Fahad Medical City; Naif A. M. Almontashiri of Taibah University; Reza Maroofian and Henry Houlden of the Neurogenetics Laboratory, UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London; Neda Mazaheri and Hamid Galehdari of Shahid Chamran University of Ahvaz, Iran; Ganka Douglas of GeneDx, Inc.; and Monique Ryan of the Royal Children's Hospital, Melbourne, Murdoch Children's Research Institute and University of Melbourne.*

*The work was supported by the National Institutes of Health, the National Institute of Neurologic Disorder and Stroke and the National Human Genome Research Institute. It was also supported by the Baylor Hopkins Center for Mendelian Genomics, and ALS Association grant and a Clinical Research Training Scholarship in Neuromuscular Disease partnered by the American Brain Foundation and Muscle Study Group.*

**Itemized Report for the Year Ended September 30, 2020**

## INTRODUCTION

Florida Statute 288.955, referred to as the Enabling Statute, sets forth certain information that is required to be included in the SFFC Annual Report. The information that follows has been organized to correspond to the sections of the Enabling Statute that address information to be included in the SFFC Annual Report. As not every section of the Enabling Statute relates to the SFFC Annual Report, only the sections of the Enabling Statute that apply are referenced herein. For convenience, the text of the Enabling Statue that describes the information to be reported in the SFFC Annual Report is set forth next to each Enabling Statute section reference.

**Florida Statute 288.955**

**Subsection (14)** **ANNUAL REPORT**
**By December 1 of each year, the corporation shall prepare a report of the activities and outcomes under this section for the preceding fiscal year. The report, at a minimum, must include:**

**Subsection (14) (a)** **A description of the activities of the corporation in managing and enforcing the contract with the grantee.**

**Scripps Florida Funding Corporation Board of Directors**

*Purpose:* To oversee the disbursement of the State's funds invested in Scripps Florida, the Florida Legislature created the Scripps Florida Funding Corporation, hereto referred to as SFFC, a non-profit entity governed by a nine-member Board of Directors and one ex-officio member.

*Membership:* Of the Board of Directors, three members each were appointed by the Governor, the House Speaker and the Senate President. Former Governor Bush's appointees are Mr. David Gury, former President and CEO of Nabi Pharmaceuticals, of Boca Raton, and Dr. Pamella Dana, Chief External Affairs Officer for Institute for the Florida Institute of Human & Machine Cognition, of Destin. Governor Crist re-appointed Mr. David Gury in March 2008 and Dr. Pamella Dana in February 2009. Former Senate President Jeff Atwater appointed Mr. Gerry Goldsmith, former Chairman of First Bank of the Palm Beaches, of Palm Beach, on November 15, 2009. Governor Scott appointed Mr. Art Wotiz, CEO of Novabone, of Jacksonville on March 25, 2013, and retained the continued service of Mr. gury and Dr. Dana as board Chair and Vice Chair, respectively. Former speaker Dean Cannon appointed Dr. Richard M. Luceri, former Vice President of Healthcare Services for JM Family Enterprises, Inc., and Speaker Will Weatherford reappointed Dr. Luceri on January 24, 2013. Speaker Weatherford appointed Mr. Mark J. Kasten, CEO of Kasten Insurance, of Tequesta on August 9, 2013. Having served more than 10 years on the Board, Mr. Gury resigned on September 30, 2019, and Dr. Dana assumed chairmanship. Having served more than their appointed time, the Directors are no longer active on the Board.

The head of the Florida Department of Economic Opportunity or his designee may serve as an ex-oficio member of the SFFC Board. The DEO has not designated a person to do so.

The SFFC receives and reviews the following reports:

- Scripps Research unaudited quarterly financial statements
- Scripps Research audited annual financial reports, including:
    - Audited financial statements of Scripps Research, including the operations of Scripps Florida.
    - Audited financial statements of Scripps Florida as a separate division, including a report on internal control and compliance in accordance with *Government Auditing Standards*.
    - A Federal Single Audit of Scripps Research in accordance with OMB Circular A-133.

  The audits are prepared by Deloitte and Touche ("D&T"), the independent auditors for Scripps Research.
- Scripps Research - Florida annual budgets
- Scripps Research - Florida Annual Report
- Scripps Research Annual Scientific Report

The independent auditor contracted by the SFFC prepares the annual not-for-profit organization tax return (Form 990) for SFFC, which is submitted to the Internal Revenue Service. This firm also has prepared a contractual monitoring and compliance audit of the Operating and Funding Agreement between TSRI and SFFC ("contractual monitoring and compliance audit") to address the *Monitoring Checklist* (Exhibit A-1 to the Funding and Program Agreement between OTTED (now known as the Department of Economic Opportunity) and SFFC). The contractual monitoring and compliance audit is completed by an independent auditor contracted by the SFFC who verifies many of the items covered in this Annual Report. Once the final grant from the State of Florida was distributed in 2013, the SFFC modified the compliance report to add items related to payments that SF is required to make to the Florida Biotech Fund reflecting 15% of royalty revenues and 15% of naming opportunities. The last compliance report reported the royalty revenues and Scripps Research sends their remittance directly to the Florida Department of Health ("FL DOH"). In Fiscal Year 2020, Scripps Research submitted $17,255 in royalty remittance to the FL DOH.

**Subsection (14) (b) An accounting of the amount of funds disbursed during the preceding fiscal year to the grantee.**

The final disbursement was made in December 2013 and consequently, the SBA and SFFC agreed to terminate their contract in early 2014. The total amount disbursed to Scripps Florida from 2003 to 2013 was $351,977,664.39, which included interest in the amount of $41,977,664.39.

**Subsection (14) (c) An accounting of the expenditures by the grantee during the fiscal year of funds disbursed under this section.**

| | | |
|---|---|---|
| Salaries & Benefits | $ | 119,374 |
| | | |
| **Total** | **$** | 119,374 |

The expense categories set forth above reflect those used by Scripps to report grant activity to grantors.

**Subsection (14)(d) Information on the number and salary level of jobs created by the grantee, including the number and salary level of jobs created for residents of this state.**

On September 30, 2020, Scripps Florida employed 507 people. Of those, 425 were full-time. The breakdown of those full-time employees is shown below.

| | |
|---|---|
| Faculty | 42 |
| Staff Scientists | 24 |
| Research Associates | 105 |
| Scientific Support | 159 |
| Administrative Support | 95 |
| Total | 425 |

In addition, on September 30, 2020 Scripps Florida employed an additional 82 employees who were part-time, research interns, or summer interns, for a total employee population of 507. Of the employees hired in this fiscal year, 42 were residents of Florida and 30 were residents of Palm Beach County.

The average salary/range for Scripps Florida employees is shown below.

| | |
|---|---|
| Faculty | $48,922 - $340,018 |
| Staff Scientists | $62,566 - $104,562 |
| Research Associates | $11,912 - $75,005 |
| Scientific Support | $4,200 - $192,296 |
| Administrative Support | $68,400 Average |

Please note that certain employees of Scripps Florida may receive additional compensation and these salary ranges might not reflect their "real" or "full" salary. The ranges set forth above do not incorporate such additional compensation. For example, a faculty member who also serves as an Associate Dean of the Graduate School will receive additional compensation for that service. In this case, administrative salary is not included in their scientific salary. Additionally, only the salary received from Scripps Research is reflected in the ranges above. This is particularly apparent for the starting range salary for research associates, several of whom earn the majority of their salary from outside funding sources.

**Subsection (14) (e) Information on the amount and nature of economic activity generated through the activities of the grantee.**

Since 2007, the Business Development Board of Palm Beach County ("BDB"), a public-private partnership established in 1982 to be the official economic development organization for Palm Beach County, has reported 48 life science expansions and relocations to the County which have created 3,674 direct jobs and retained 519 jobs. This has resulted in over $330 million in capital expenditures in the life sciences and healthcare industries. Scripps Florida remains a steadfast supporter of the many requests for tours and information for the BDS's recruitment visits.

In 2019, the BDB reported that there are ten companies coming to Palm Beach County within the life science industry, creating over 350 jobs, and the organization has assisted over a dozen life science companies to grow, making direct investments of over $100M into the local economy. A new

proposed life science accelerator is planned for Jupiter, Gift of Life opened the Nation's first stem cell collection center in Boca Raton, and Expansion Therapeutics is creating cures for RNA-mediated diseases. Other companies that made moves or expanded in Palm Beach County included Algafeed, Alphazyme, Capzer Pharmaceuticals, Cytonics, Detraxi, Beacon of Hope CRO, 20Lighter, and Secret Sequence. The BDB also reported that the largest life sciences Series A investments in Florida for 2018-19 were in Palm Beach County, including Expansion Therapeutics and X-Vax, both exceeding $55M each.

In June 2020, the BDB's Robert Mino, Vice President of Life Sciences, announced that 10 new life science companies have relocated to or expanded in Palm Beach County, creating more than 1,000 high salary jobs over the past six months. Currently, 30 additional companies are planning announcements by the end of 2020, which would create 1,600 more jobs. Other exciting updates for the sector:

- For the first time in 21 years, BioFlorida Annual Conference will be hosted in Palm Beach County. Life science leaders from around the world will see the County's innovation in-person.
- The BDB has continued "Post Doc Career Talks" with local academic institutes such as Scripps, FAU, Lynn, and Keiser. This has resulted in several local hires, retaining graduated talent locally.
- A tri-county call with the State of Florida Drugs, Devices, and Cosmetics, and a dozen pharmacies, pharmaceutical manufacturers, and other stakeholders, was hosted by the BDB to prepare Florida's drug supply for the hurricane season in the age of Covid-19

In September 2020, the BDB announced that Seven Kings Holdings, Inc. is building out laboratory space within walking distance of the Scripps Research Institute, Max Planck Florida Institute for Neuroscience, and Florida Atlantic University's Jupiter Campus. The Jupiter Center for Discovery will bring much needed high end laboratory space to Palm Beach County, a competitive edge that will attract more life science companies as they leave biotech hotspots like Cambridge, MA and Torrey Pines, CA.

The Business Development Board of Palm Beach County (BDB) worked with Ray Graziotto, President and CEO of Seven Kings Holdings on making the necessary connections and providing support through this new development. This project will bring new, high-end lab space in Jupiter, 25,000 s.f. of space transformed, accommodations for approximately 50 researchers, in addition to anchor companies. flexible lease terms for early stage life science companies, more research-specific space to attract research, biotech and life science tenants, and Deluge Biotechnologies will be a future tenant, along with a handful of others that have expressed intent to commit.

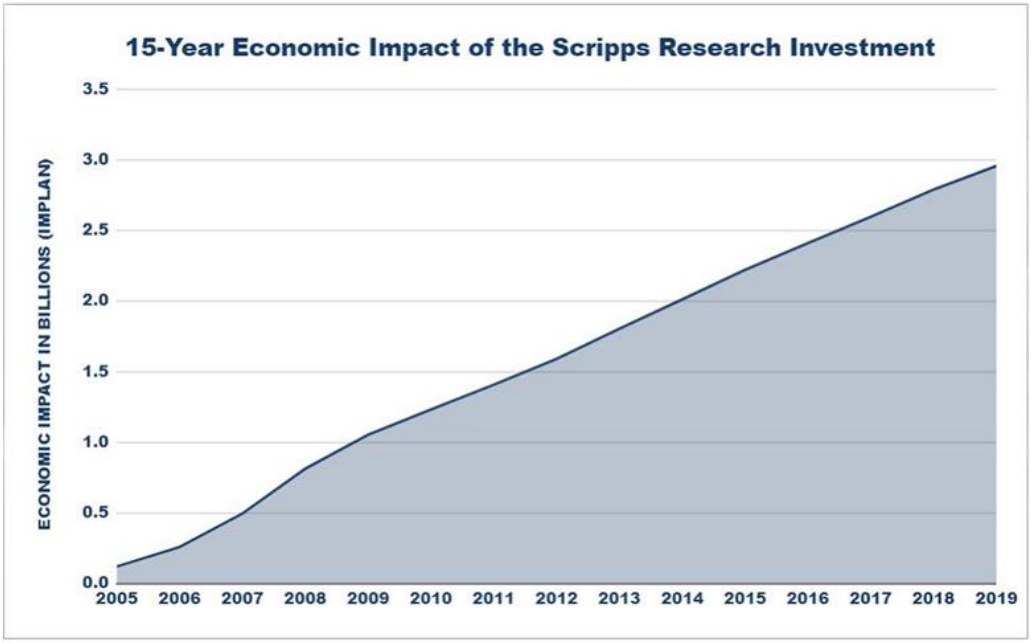
For more information, visit: https://www.bdb.org/index.php?src=pages&ref=lifesciences

**Subsection (14) (f) An assessment of factors affecting the progress toward achieving the projected biotech industry cluster associated with the grantee's operations, as projected by economists on behalf of the Executive Office of the Governor.**

The industry standard IMPLAN (Economic Impact Analysis for Planning) model was used for an economic impact study. It relied upon expenditures by the Florida campus as its input and academic research institute consultant Cary Thomas, MBA, CMA, performed the analysis. The IMPLAN model considers direct spending on wages, services and supplies, and then calculates indirect spending by

businesses in the company's supply chain, and induced spending by workers on items such as real estate, meals, taxes, insurance and other items.

The IMPLAN analysis found the following: the launch of the Florida campus of Scripps Research has produced an economic impact of $3 billion since the nonprofit biomedical institute opened an East Coast branch 15 years ago, this $3 billion figure represents a fairly conservative multiplier of 2.42, more than $1.2 billion has been directly spent by the Florida institute through the 15-year period, and, cumulatively since 2004, every dollar invested in Scripps Florida has returned $6.




Not included in this figure is the fact that Scripps Research's presence has seeded and attracted other local life science research and development companies. Expansion Therapeutics, which raised $60 million to develop innovative therapies for conditions including ALS and muscular dystrophy in 2017 and 2018, Excovery and Beacon Pharmaceuticals, not to mention the Max Planck Florida Institute for Neuroscience, all exist in Palm Beach County in proximity to Scripps Research. These companies are not accounted for in the report. Another spinoff, Xcovery, now based in Palm Beach Gardens, developed an anti-cancer compound, Ensartinib, which is being investigated for the treatment of ALK-positive non-small cell lung cancer. It recently completed enrollment for phase 3 clinical trials. That impact is likewise not included in the study. Founder Chris Liang, PhD, was one of the first scientists recruited to Scripps Research's Florida campus in 2004.

In addition to the IMPLAN economic analysis study, Scripps Research looked back at the intellectual property created from its discoveries. That analysis reveals a total of 162 clusters of patent applications have been filed on technology developed at the Jupiter campus, with each cluster containing 1-6 separate patent applications.

**Subsection (14) (g) A compliance and financial audit of the accounts and records of the corporation at the end of the preceding fiscal year conducted by an independent certified public accountant in accordance with the rules of the Auditor General.**

A 9/2019 trial balance was completed by Scott L. Porter, C.P.A. of Caler, Donten, Levine, Cohen, Porter & Veil, P.A. and reported the following for the 2019 tax return:

| | |
|---|---|
| Insurance | $25,799.75 |
| Office Supplies & Expenses | $175.17 |
| Telephone | $1,014.24 |
| Public Meeting Notices | $93.03 |
| Professional Fees - legal | $6,052.00 |
| Professional Fees – accounting & auditing | $12,555.00 |
| Professional Fees - consulting | $5,175 |
| Bank Service Charges | $49.95 |
| **Bank Balance as of 9/2019** | **$37,885.45** |

The 9/2020 balance is contingent upon year-end bills and will be solidified by 12/31/2020.

**Subsection (14) (h) A description of the status of performance expectations under subsection (9) and the disbursement conditions under subsection (10).**

**Subsection (9) PERFORMANCE EXPECTATIONS**

**Subsection (9) (a) The number and dollar value of research grants obtained from the Federal Government or sources other than this state.**

| Grant Number | Sponsor | New / Renewal | Award Amount |
|---|---|---|---|
| 1R01 CA249180-01 | National Cancer Institute | New | $ 538,374 |
| 1R01 CA221948-02 | National Cancer Institute | Renewal | $ 79,617 |
| 1R01 CA221948-02 | National Cancer Institute | Renewal | $ 156,877 |
| 1R01 CA221948-02 | National Cancer Institute | Renewal | $ 45,934 |
| 3R01 CA174844-06 | National Cancer Institute | Renewal | $ 92,500 |
| 7R01 CA223823-02 | National Cancer Institute | Renewal | $ 199,922 |
| 7R01 CA227073-02 | National Cancer Institute | Renewal | $ 173,142 |
| P01 CA154303-08 | National Cancer Institute | Renewal | $ 42,643 |
| R01 CA223823-03 | National Cancer Institute | Renewal | $ 251,678 |
| R01 CA227073-03 | National Cancer Institute | Renewal | $ 226,091 |
| 1K99 EY030554-01 | National Eye Institute | New | $ 94,443 |
| 1R56 AG065986-01 | National Institute of Aging | New | $ 462,500 |
| P01AG062413-02 | National Institute of Aging | Renewal | $ 148,118 |
| 1R01 AI153298-01 | National Institute of Allergy and Infectious Diseases | New | $ 22,246 |
| 1R01 AI154989-01 | National Institute of Allergy and Infectious Diseases | New | $ 458,896 |
| 1R21 AI152836-01 | National Institute of Allergy and Infectious Diseases | New | $ 231,250 |
| 1U19 AI149646-01 | National Institute of Allergy and Infectious Diseases | New | $ 46,250 |
| 1U19 AI149646-01 | National Institute of Allergy and Infectious Diseases | New | $ 4,455 |

| Grant Number | Sponsor | New / Renewal | Award Amount |
|---|---|---|---|
| 1U19 AI149646-01 | National Institute of Allergy and Infectious Diseases | New | $ 462,500 |
| 1U19 AI149646-01 | National Institute of Allergy and Infectious Diseases | New | $ 462,500 |
| 1R01 AI119043-05 | National Institute of Allergy and Infectious Diseases | Renewal | $ 182,365 |
| 1R01 AI119043-05 | National Institute of Allergy and Infectious Diseases | Renewal | $ 105,635 |
| 1R01 AI119564-04 | National Institute of Allergy and Infectious Diseases | Renewal | $ 20,472 |
| 1R01 AI127677-4 | National Institute of Allergy and Infectious Diseases | Renewal | $ 325,098 |
| 1UM1 AI126623-04 | National Institute of Allergy and Infectious Diseases | Renewal | $ 287,525 |
| 3R01 AI129868-04 | National Institute of Allergy and Infectious Diseases | Renewal | $ 381,098 |
| 3R01 AI129868-04 | National Institute of Allergy and Infectious Diseases | Renewal | $ 293,541 |
| 5K99 AI138860-02 | National Institute of Allergy and Infectious Diseases | Renewal | $ 129,870 |
| 5R01AI132378-04 | National Institute of Allergy and Infectious Diseases | Renewal | $ 92,500 |
| 5R03 AI144714-02 | National Institute of Allergy and Infectious Diseases | Renewal | $ 46,250 |
| R01 AI141592-02 | National Institute of Allergy and Infectious Diseases | Renewal | $ 100,010 |
| U54 AI150472-08 | National Institute of Allergy and Infectious Diseases | Renewal | $ 285,472 |
| 1R01 DK124870-01 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | New | $ 436,902 |
| 1R01 DK124870-01 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | New | $ 68,278 |
| 1R01 DK107239-03 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | Renewal | $ 124,198 |
| 1R01 DK107239-03 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | Renewal | $ 124,196 |
| 1R01 DK112759-03 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | Renewal | $ 75,639 |
| 2R01 DK105954-05 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | Renewal | $ 575,350 |
| R01 DK117655-02 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | Renewal | $ 176,795 |
| R01 DK117655-02 | Nat. Inst. of Diabetes, Digestive & Kidney Diseases | Renewal | $ 176,795 |
| 1R01 GM130624-01 | National Institute of General Medical Sciences | New | $ 28,500 |
| 1R35 GM134954-01 | National Institute of General Medical Sciences | New | $ 795,502 |
| 1R35 GM136323-01 | National Institute of General Medical Sciences | New | $ 868,507 |
| 3R35 GM134954-01 | National Institute of General Medical Sciences | New | $ 150,000 |
| 1R01 GM088278-09 | National Institute of General Medical Sciences | Renewal | $ 43,699 |
| 1R01 GM129436-02 | National Institute of General Medical Sciences | Renewal | $ 29,775 |
| 3R35 GM128895-02 | National Institute of General Medical Sciences | Renewal | $ 100,000 |
| 5UL1 TR002550-03 | National Institute of Health | Renewal | $ 26,202 |
| 2R01 MH105482-06 | National Institute of Mental Health | Renewal | $ 480,000 |
| 2R01 MH113648-04 | National Institute of Mental Health | Renewal | $ 686,767 |
| 5R01 MH119541-02 | National Institute of Mental Health | Renewal | $ 564,405 |
| 5R21MH117485-03 | National Institute of Mental Health | Renewal | $ 10,138 |
| 1R01 NS110307-01 | Nat. Institute of Neurological Disorders and Stroke | New | $ 454,829 |
| 1R35 NS116846-01 | Nat. Institute of Neurological Disorders and Stroke | New | $ 1,147,500 |
| 1R41 NS113694 | Nat. Institute of Neurological Disorders and Stroke | New | $ 56,633 |

| Grant Number | Sponsor | New / Renewal | Award Amount |
|---|---|---|---|
| 1R41 NS113694 | Nat. Institute of Neurological Disorders and Stroke | New | $ 66,753 |
| 1UG3 NS116921-01 | Nat. Institute of Neurological Disorders and Stroke | New | $ 277,500 |
| 4R33 NS099417-03 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 310,198 |
| 5P01 NS099114-04 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 119,503 |
| 5P01 NS099114-04 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 249,341 |
| 5R01 NS102414-04 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 300,491 |
| 5R01 NS112534-02 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 439,031 |
| 5UH3 NS096833-04 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 67,869 |
| 5UH3 NS096833-04 | Nat. Institute of Neurological Disorders and Stroke | Renewal | $ 22,590 |
| 1R01 DA049544-01 | National Institute on Drug Abuse | New | $ 721,617 |
| 1R01 DA045020-03 | National Institute on Drug Abuse | Renewal | $ 247,950 |
| 1R61 DA047039-02 | National Institute on Drug Abuse | Renewal | $ 177,774 |
| 1UG3 DA048385 | National Institute on Drug Abuse | Renewal | $ 462,500 |
| 5R01 DA036596-07 | National Institute on Drug Abuse | Renewal | $ 552,841 |
| 5R01 DA046204-03 | National Institute on Drug Abuse | Renewal | $ 271,708 |
| 5R01 DA048036-02 | National Institute on Drug Abuse | Renewal | $ 641,882 |
| 5R01 DA048036-02 | National Institute on Drug Abuse | Renewal | $ 641,882 |
| R01 DA048490-02 | National Institute on Drug Abuse | Renewal | $ 262,545 |
| ABBVIE/SFP-0580 | Abbvie Inc. | New | $ 160,000 |
| BMS | Bristol Meyers Squibb | New | $ 350,764 |
| W81XWH-19-1-0418 | Department of Defense | New | $ 185,000 |
| W81XWH-19-1-0570 | Department of Defense | New | $ 971,244 |
| W81XWH-19-1-0718 | Department of Defense | New | $ 658,735 |
| DOOR/SFP-0215 | Door Pharmaceuticals, LLC | New | $ 187,794 |
| LILLY/SFP-0073 | Eli Lilly | New | $ 535,323 |
| EXPANSION/SFP20 | Expansion Therapeutics | Renewal | $ 306,675 |
| FCBTR AWARD | FL Center for Brain Tumor Research | New | $ 62,500 |
| FLDOH 20K03 | FL Department of Health | New | $ 32,096 |
| NSF/1945468 | National Science Foundation | New | $ 267,991 |
| NSF/2033939 | National Science Foundation | New | $ 199,844 |
| PFIZER/SFP-0075 | Pfizer | New | $ 578,124 |
| GATES/OPP1196704 | The Bill and Melinda Gates Foundation | New | $ 100,108 |
| GATES/OPP1196704 | The Bill and Melinda Gates Foundation | New | $ 72,227 |
| THERMO/2018-0872 | Thermo Fischer | New | $ 207,438 |
| VOVA/SFP-0128 | VOVA IDC LLC | New | $ 60,911 |
| | **Total Awards** | | **$ 24,421,131** |

Note: In the above presentation, some awards are divided among more than one faculty member, and in those cases the individual award allocations are shown to provide a detailed accounting. Amounts shown are the first-year award amount for those "New" awards, and the respective continuing yearly amount for "Renewal" awards.

**Subsection (9) (b) The percentage of total research dollars received by TSRI from sources other than this state which is used to conduct research activities by the grantee in this state.**

The percent of research funding from sources other than SFFC was 97%.

**Subsection (9) (c) The number or value of patents obtained by the grantee**.

10 foreign and domestic patent applications were filed and nine U.S. patents were issued. Since inception, 170 "families" of patent applications have been filed covering Scripps Florida technology, with each family containing one - six patent applications.

**Subsection (9) (d) The number or value of licensing agreements executed by the grantee.**

Six license agreements were executed with respect to Scripps Florida technologies in FY 2020.

**Subsection (9) (e) The extent to which research conducted by the grantee results in commercial applications.**

Because of the early stage of the technology being developed at Scripps Florida, no commercial applications have emerged to date. Currently, Scripps Florida is actively engaged in developing novel therapeutics against SARS-CoV-2 which could benefit from accelerated development timelines. Moreover, as noted in previous Annual Reports, several research tools developed at Scripps Florida continue to be available commercially through various licensing arrangements.

**Subsection (9)(f) The number of collaborative agreements reached and maintained with colleges and universities in this state and with research institutions in this state, including agreements that foster participation in research opportunities by public and private colleges and universities and research institutions in this state with significant minority populations, including historically black colleges and universities.**

The Scripps Research Institute has developed a template entitled the Joint Cooperation Agreement ("JCA") to encourage and support research collaborations with Florida institutions. Provisions are included to make it easier to collaborate on filing patents for jointly developed technologies and to share revenues from commercialized innovations. By executing these agreements in advance, TSRI expects to streamline the scientific collaboration process between Florida organizations and Scripps Florida as they work together on biomedical research. Nine Florida institutions have currently executed this formal agreement with TSRI: Florida International University, University of Florida, Florida Atlantic University, University of Central Florida, University of Miami, Florida State University, Nova Southeastern University, University of South Florida and Max Planck Florida Institute. Scripps

scientists have also participated in formal scientific meetings with colleagues at Florida foundations, colleges and universities.

**Subsection (9) (g) The number of collaborative partnerships established and maintained with businesses in this state.**

Scripps Florida continues to maintain collaborative relationships with these Florida based biotechnology companies:

Florida Power and Light Scripps is collaborating with Florida Power and Light, a Juno Beach, Florida-based power utility that is the principal subsidiary of NextEra Energy Inc., to develop novel and proprietary technology which may yield cheaper and more effective ways at producing fuels and other commodities from natural gas.

Opko Health Opko Health, Inc., based in Miami, is a publicly traded healthcare company involved in the discovery, development, and commercialization of pharmaceutical products, vaccines and diagnostic products. Opko and Scripps are currently collaborating in three major areas: the area of novel diagnostic products to detect Alzheimer's and other diseases, the development of novel drug candidates to treat Parkinson's Disease, and the discovery of novel antibiotics.

Vova Ida Therapeutics is a Palm beach County-based company founded in 2013 to commercialize research from Corinne Lasmeza's lab at Scripps Florida. Lasmeza is a professor in the Department of Infectious Diseases and her lab researches neurodegenerative diseases. The company is developing drugs to treat age-related neurodegenerative diseases, such as Alzheimer's disease.

Dyadic International - A collaborative effort between scientists at Scripps Florida and Dyadic was established to provide a complete annotation of the genome of Dyadic's proprietary fungal organism, Chrysosporium lucknowense ("C1"). The knowledge gained from this effort is expected to facilitate further development of the C1 Host Technology as a robust platform for the discovery, development and production of various materials for medical and industrial applications. Furthermore, this collaboration promotes the development of a successful biotechnology cluster in South Florida.

Emmune, previously Immunathon, was founded in 2015 in Palm Beach County to commercialize technology from Mike Farzan's lab at Scripps Florida. The company is engaged in the development and commercialization of novel approaches for the treatment and prevention of HIV infection.

Expansion Therapeutics, based on Disney lab technology at Scripps Florida with research facility in Jupiter, is focused on development of therapeutics for RNA mediated diseases.

Deluge Biotechnologies, located in Jupiter, founded in 2017 based on technologies from Paegel and Kodadek labs at Scripps Florida, employs DNA encoded epitope surrogate technology to develop disease diagnostics.

CALM Therapeutics is developing novel therapeutics to treat Prader-Willi syndrome.

During the past year, Scripps Florida has established many partnerships with Florida businesses and small business entities. A full list of all of those companies may be found in the Scripps Florida Annual Report, starting on page 79 and ending on 84.

**Subsection (9) (h) The total amount of funding received by the grantee from sources other than the State of Florida.**

Since inception, Scripps Florida has been awarded $643,848,989 in grants and sponsored research funding from state and federal agencies (including the NIH), foundations, pharmaceutical companies and other grantors. In addition, the County of Palm Beach provided $210 million to Scripps for construction of the permanent facility.

Funding received by Scripps Florida from sources other than the State of Florida for FY 2020:

| | |
|---|---|
| Other Revenue Sources | $ 1,330,837 |
| Grant Awards | $ 14,172,338 |
| Contributions* | $ 1,287,463 |

**This amount was determined in accordance with generally accepted accounting principles. Therefore, certain non-cash items, such as promises to give, are reflected at their estimated net realizable value.*

**Subsection (9) (i) The number or value of spin-off businesses created in this state as a result of commercialization of the research of the grantee.**

The companies that spun off from Scripps Florida technology and an additional Florida companies located in Jupiter to access Scripps Florida are described in Subsection (9)(g). No attempt has been made by Scripps to assign a value to these spinoffs.

In February 2011, CuRNA, one of the first spin-offs from Scripps Florida, was purchased by Miami-based Opko Health for $10,000,000. In November 2012, Envoy Therapeutics was purchased by Japan-based Takeda for $140,000,000, and Padlock Therapeutics was purchased by New York-based Bristol-Meyers Squibb for up to $600,000,000.

**Subsection (9) (j) The number or value of businesses recruited to this state by the grantee.**

To assign a numerical value to business recruitment activities is virtually impossible. Scripps Florida is extensively involved in local, state and national efforts to promote and develop the biotech industry in Palm Beach County and the State of Florida. See analyses at Subsections (14)(e and f).

**Subsection (9)(k) The establishment and implementation of policies to promote supplier diversity using the guidelines developed by the Office of Supplier Diversity under s. 287.09451 and to comply with the ordinances, enacted by the County and which are applicable to this biomedical research institution and campus located in this state.**

Scripps Florida has adopted the following Mission and Vision Statements for Supplier Diversity:

Scripps Research is committed to maintaining an equitable and competitive business environment. As part of this commitment, we work to develop procedures and initiatives that will help ensure that all companies receive fair consideration. Scripps Research recognizes contractor and supplier diversity as an important component of its overall business effort and will continue to take all necessary affirmative

steps to assure that small and minority businesses, women's business enterprises, and labor surplus area firms are used when possible for the procurement of goods and services.

The TSRI Procurement Department, led by Mr. Erik Duffey, Director, Florida Procurement, continues to pursue opportunities to partner with the diverse business community. Scripps Florida continues to participate in county, state and national diverse supplier shows. These shows help Scripps Florida to identify diverse businesses that can provide goods and services to the institute at a competitive price. Participation in these shows has resulted in partnerships with local companies that provide furniture, pipette calibrations, refrigeration services, relocation services, dry ice services, landscaping and irrigation services, building maintenance services, printing services, shredding services and more.

**Subsection (9) (l) The designation by the grantee of a representative to coordinate with the Office of Supplier Diversity.**

Mr. Adrian Orozco serves in this position as the Supplier Diversity Coordinator. Mr. Orozco represents Scripps in working with small and minority business enterprises in the State of Florida, and is actively involved in many state and local supplier diversity outreach programs.

**Subsection (9) (m) The establishment and implementation of a program to conduct workforce recruitment activities at public and private colleges and universities and community colleges in this state which request the participation of the grantee.**

Scripps Florida has continued its workforce recruitment efforts with Florida's higher education institutions throughout the state.

| University / Institution | Event | Date |
|---|---|---|
| Florida Atlantic University | FAU Graduate and Professional School Fair | 10/24/2019 |
| Florida Department of Veterans Affairs | Paychecks for Patriots Veterans Career Fair | 11/13/2019 |
| Florida Memorial University | Florida Memorial Career & Grad School Fair | 11/16/2019 |
| University of Central Florida | UCF 2020 Spring Career Expo | 01/28/2020 |
| Florida Atlantic University | FAU Internship & Study Abroad Showcase | 01/30/2020 |
| Florida Atlantic University | FAU Career Expo - Spring 2020 | 02/13/2020 |
| University of Miami | Spring Career Expo 2020 | 02/25/2020 |
| University of South Florida | Spring 2020 Bulls Connect (campus-wide career and internship fair) | 02/05/2020 |
| 12 Public Universities | Florida Statewide Virtual Career Fair - Career Eco Virtual Career Fairs | 06/17/2020 |

**Subsection (10) DISBURSEMENT CONDITIONS**

**Subsection (10)(a) Demonstrate creation of jobs and report on the average salaries paid.**

On September 30, 2020, Scripps Florida employed 507 people (425 full-time and 82 part-time). See reply to Subsection (14) (d).

**Subsection (10)(b) Beginning 18 months after the grantee's occupancy of its permanent facility, the grantee shall annually obtain $100,000 of non-state funding for each full-time equivalent tenured-track faculty member employed at the Florida facility.**

There were 42 tenure track faculty employed on September 30, 2020 and the total award value (the initial award amount for new awards and the annual increment for renewal awards) was $24,421,131, therefore in this fiscal year each Scripps Florida faculty obtained about $581,455 in non-Florida funding.

This represents 22 new grant awards and 51 renewal grant awards from the National Institutes of Health (NIH) and 16 new grant/contract awards and 1 renewal grant/contract awards from non-state entities other than NIH. See Section 9(a) for a complete list of awards.

**Subsection (10) (c) No later than 3 years after the grantee's occupancy of its permanent facility, the grantee shall apply to the relevant accrediting agency for accreditation of its Florida graduate program.**

The re-accreditation of the Scripps Ph.D. program was successfully completed in early 2011, which is approximately two years after Scripps Florida's occupancy of its permanent facility.

Scripps Research began planning for the reaccreditation process in January 2017. A steering committee was appointed, a plan and timeline were adopted, and the first meeting was held in February 2017. The committee includes the Deans, Graduate Office staff and key faculty who serve as chairs on self-study committees from both campuses. On August 17, 2018, the WSCUC liaison, Richard (Dick) Osborn, visited the California campus and hosted a bicoastal workshop on preparing for the Institutional Report and the Accreditation Visit. The Accreditation Visits to Scripps Research by the evaluation team took place August 28-29, 2019 on the Florida campus and Sept 17-19, 2019 on the California campus.

The site visits occurred as schedule without a hitch. On February 14, 2020, Dean Philip E. Dawson and Director Dawn L. Eastmond attended the WSCUC Commission Meeting to address any lingering questions and concerns reviewing our reports and exhibits as well as the evaluation teams' reports. Two weeks later, President Schultz received a letter memorializing the accreditation. The letter read as follows:

Actions

1. Receive the Accreditation Visit team report
2. Reaffirm accreditation for a period of ten years
3. Schedule the next reaffirmation review with the Offsite Review in spring 2029 and the Accreditation Visit in fall 2029
4. Schedule the Mid-Cycle Review to begin May 1, 2025
5. Schedule a Progress Report to be submitted by October 1, 2024 to address all recommendations in this letter

In addition, the Commission commended TSRI in particular for the following:

1. TSRI has a clear, strategic focus to its plans and future directions. Faculty, staff and students understand the leadership's vision and view it as a strength of the institution. The Graduate

Program lies squarely at the heart of TSRI's mission, building on and reinforcing the strength of the faculty and their research productivity and expertise.

2. TSRI has become a model of a multidisciplinary graduate program. Basic and translational research across multiple disciplines prepares graduates for a range of careers much broader than typical doctoral programs. The usual tension between discovery and application in science is a strength here, not a challenge.
3. Assessment and evaluation practices are widely embraced by the deans, faculty, and staff in the program and demonstrate nimble responsiveness to student and disciplinary needs. In an impressive cycle of organizational learning, these evaluation practices continue to evolve to better understand and adapt to student needs. These exemplary processes should be sustained and expanded as needs arise.
4. TSRI has a strong commitment to using data and evidence for decision making, supported by the Graduate Office and its institutional research function, which is well-developed and makes effective use of data analytics to communicate information to faculty and administrators.
5. The campaign to endow graduate fellowships is well-considered and appears poised for success. The campaign is widely viewed within the organization as a transformative opportunity. Focus on endowing the Graduate Program confirms the centrality of the program to the TSRI while at the same time preparing for even broader fundraising efforts.
6. There is widespread faculty participation in admissions, curriculum development, and professional development. The faculty have established feedback loops to rapidly respond to issues with the curriculum when they emerge, in order to maintain the world-class status of its doctoral program.
7. The institution is committed to increasing diversity across the organization and has taken steps to recruit more women and underrepresented minorities. The leadership team's commitment to creating an inclusive, safe, and tolerant campus is evidenced by the resources, policies, and programs put in place to promote of this goal.
8. TSRI has made impressive strides in bicoastal integration. Progress had been made in creating a unified admissions process, integrating more Florida faculty into teaching and student advisory committees, and in integrating professional development and co-curricular activities across the campuses.

The Commission requires the institution to respond to the following issues:

1. As TSRI develops plans to increase the size of its graduate program, careful thought should be given to the size and function of the supporting programs, such as the Graduate Office and the Career and Postdoctoral Office. These programs have become central to the development and success of the students.
2. TSRI should continue to prioritize increasing diversity within the Graduate Program. The institution is encouraged to seek out and develop innovative practices used at other, similar institutions, to continue progress in this area.
3. The Committee for Gender Parity and Faculty Engagement should continue its work, with the goals of evaluating and improving the cultural environment of the institute. TSRI should continue to build on its efforts begun under Title IX implementation to improve campus climate and "become the place where inclusion is a habit and equity is a priority."
4. TSRI should expand activities to improve the sense of community for students, including more opportunities for faculty and students to engage outside the labs.

5. Bicoastal integration should remain a priority. TSRI should continue to explore initiatives to improve the quality of online learning, such as faculty training in online delivery, and investing in technology to improve course delivery and student engagement.
6. Staffing levels in the area of philanthropy may be low by industry standards and relative to the Institute's fundraising aspirations. The team recommends continued efforts to sustain and expand the initial success of the endowment campaign.

In taking this action to reaffirm accreditation, the Commission confirmed that TSRI addressed the three Core Commitments and successfully completed the two-stage institutional review process conducted under the 2013 Standards of Accreditation.

*U.S. News & World Report* has listed TSRI's Graduate Program, which operates on both of its campuses and enrolls 40 to 50 students per year, among its top ten Best Grad Schools for 19 straight years.

**Subsection (10) (d) The grantee shall purchase equipment for its Florida facility as scheduled in its contract with the corporation.**

The Scripps Florida business plan requires $10 million in equipment purchases within 18 months of occupancy of the permanent facility and Scripps occupied the permanent facility on March 31, 2009, so the effective date for the $10 million required equipment purchase was September 30, 2010. The amount of equipment purchased as of September 30, 2010 was $10.7 million, thereby meeting the required amount.

Additionally, Scripps Florida was required to purchase a total of $45m of equipment over the term of the contract. The total cost of equipment purchased by Scripps Florida from inception through contract year end January 29, 2013 was $53,895,431 and thus the requirement was fully satisfied.

$4,586,957 of equipment was acquired with non-State sources this fiscal year.

**Subsection (10)(e) No later than 18 months after occupying its permanent facility, the grantee shall establish a program for qualified graduate students from Florida universities permitting them access to the facility for doctoral, thesis-related research.**

The Ph.D. program on the Florida campus was established in 2005 as part of Scripps Research Skaggs Graduate School in Chemical and Biological Sciences, well ahead of the September 2010 deadline, which was 18 months after the anticipated occupancy of the permanent facility.

Thus far, 55 students have completed their PhD on the Florida campus. The students worked on a number of research projects including total synthesis of important drugs, addiction to nicotine, and control of gene expression. More than 65% of the students have publications at the time of graduation and they completed the program in an average of 5.2 years.

Scripps Research also has a joint M.D./Ph.D. Program with Florida Atlantic University, an eight-year program that provides academically strong students the opportunity to earn both a M.D. and a Ph.D. in the chemical and biological sciences.

Please note the outstanding program and analysis of its admission data at the following site:
http://education.scripps.edu/accreditation/student_achievement/admissions_data.html

**Subsection (10) (f) No later than 18 months after occupancy of the permanent facility, the grantee shall establish a summer internship for high school students.**

The Education Outreach and Community Engagement (EOCE) Programs at the Florida Campus of Scripps Research were established in 2005 (four years before the occupation of the permanent facility), thanks to the great generosity of the William R. Kenan, Jr. Charitable Trust, to benefit the Palm Beach Community and the trainees. The High School Student Summer Internship Program (Kenan Fellows) is one of many initiatives implemented by Scripps Research EOCE Programs. These initiatives strongly support Palm Beach County's elementary, middle, and high school students, as well as teachers and other members of the community. Throughout the years, the program has evolved to also include outreach initiatives for undergraduate students, especially those attending Florida colleges and Floridians who move away for college. Lastly, Scripps Research graduate students and postdoctoral fellows have benefited from the EOCE Programs by obtaining science communication and teaching skills as well as mentoring experience.

The goals of Scripps Research EOCE Programs are to promote careers in biomedical research in younger generations, to create awareness in the community about the importance of supporting basic scientific research and drug discovery, and to train the next generation of scientists.

The COVID-19 pandemic did not allow Scripps to offer the training experience required for high school interns to thrive in their laboratories in Summer 2020. Based on this reality, they offered various webinars and training opportunities virtually throughout the summer that are listed below.

**First Interactive Resources for Students and Teachers (FIRST)**
Scripps Research introduced its Fully Interactive Resources for Students and Teachers (FIRST) initiative that features virtual webinars and workshops specifically for high school students, teachers, and undergraduate students. This resource provides a platform to interact with our scientists, learn about research careers, and access hands-on activities that bring science to life in your home and classroom.
*For high school students, the following webinars were features:*

- Color Changing Cabbage Science Demonstration

Alena Vasquez a graduate student in the chemistry department lead this webinar. She demonstrated how a pigment in red cabbage can be used as an indicator solution to figure out the pH of common household items.

- Separating Colors Science Demonstration

Madeline Balzarini, a graduate student at Scripps Research, lead this webinar in which she demonstrated the role of solvents in separating different ink samples using chromatography.

For undergraduate students, the webinars were divided into three tracks: (1) applying to graduate school; (2) career options with a PhD; and (3) research talks given by graduate students and postdoctoral fellows. Each track consisted of 4-6 webinars that took place every Tuesday starting in June. The format of the webinar was 20-minute introduction of the topic and 30 minutes of questions and interactions with the speaker(s). All lectures and collateral material are posted on our CANVAS page: https://scrippsresearch.instructure.com/courses/314, and the Academic Year Research Internship for Undergraduates information may be found at https://education.scripps.edu/undergraduate/academic-year-research/ayriu/

Webinar samples taught by Scripps Research PIs, graduate students, and member of the Office of Graduate Studies were:

Career Options with a Ph.D. (Career Options track) The Ph.D. is the route to many destinations, and those holding the doctorate follow diverse career paths. The goal of this workshop is to raise awareness of the many opportunities for a Ph.D. recipient. Speakers included Matthew Busse, Ph.D., Database Curator at the La Jolla Institute for Allergy and Immunology; Sharon Kwan, Ph.D., Officer in the Technology Development Office at Scripps Research, Luke Wiseman, Ph.D., Assistant Professor at Scripps Research, and Leyna Zhao, Ph.D., Scientist at Acea Biosciences. The workshop was an informal discussion, where the panelists described the paths to their chosen careers and the skills required to be successful in that field.

Goth Math? The Role of a Biostatistician. (Career Options track) Do you love your math classes as much as your biology and chemistry ones? Have you considered a career in biostatistics and data science? Biostatisticians typically address healthcare topics, either in the private or public sectors, and work in an office environment. A biostatistician is expected to design, analyze, and implement targeted statistical studies, which are geared to further medical knowledge and the improve research efforts in public health. For example, by compiling and analyzing the outcomes of medical procedures, they can report any known side effects to those who undergo the procedure in the future. Join us to learn about the responsibilities of a biostatistician, how they support the biomedical research enterprise, and the educational requirements needed for this career.

How to Read a Scientific Paper (Research Talks track) In this workshop, the CREATE (Consider, Read, Elucidate the hypotheses, Analyze and interpret the data, and Think of the next Experiment) method to engaged students with primary literature. Students will develop skills for understanding and designing scientific research. The students will have the opportunity to select the papers used for the presentation and will get to see the evolution of research over a long period of time.

**K-12 and Public Science Education Programs**

In addition to the internship programs for high school and undergraduate students, Scripps Research support the following K-12 and public education programs developed through the efforts of our Office of Education Outreach and Community Engagement, faculty, and research staff. Descriptions of all these programs as well as a list of the latest events are below:

School visits, partnerships, and community outreach – This section comprises many different types of educational outreach events and activities. Schools and non-profit organizations that run educational and career related programs for middle and high school students frequently reach out to us to lead a session or a hands-on activity. Significantly more students and members of the public are reached when we partner with these organizations and their initiatives. Many lessons have been created by the Education Outreach Office through the years and they are presented at these events. Examples of these lessons are: What Makes You 'You'- DNA Isolation, Drug Discovery, Model Organisms, Introduction to Science, The Basic You - An Introduction to Genetics, and Discovering the Brain and its Functions. Lessons are also offered in Spanish.

The Science Family Nights series, as well as programs created in partnership with Max Planck Florida Institute of Neuroscience ("MPFI"), Palm Beach State College, and the Women's Foundation of Palm Beach County are other outreach initiatives that we have led. We hope the William R. Kenan, Jr. Charitable Trust shares our vision of creating strong partnerships with other Palm Beach County

organizations to raise awareness of the importance of science to our well-being as a society. Our plan is to continue to build upon these relationships in future years.

Diversity Visitation Event for Research and Graduate Education (DiVERGE) – This program that is geared toward undergraduate students, particularly from underrepresented and underserved backgrounds in the sciences, interested in biomedical research. It allows selected students from all over the nation to learn about ongoing research projects at TSRI, internship opportunities and the Graduate Program, crafting successful graduate school and internship applications, writing an effective personal and research statement, constructing and giving a compelling self-introduction, and science identity and the culture of science. In the future, we hope to continue to host this important program as we have found that underrepresented and underserved minorities are in need of additional training in order to become more competitive candidates for nationally ranked graduate programs.

Lending Library – This program offers teachers in the county and TSRI scientists the opportunity to borrow scientific equipment (e.g. microscopes, specimen slides, pipettes) that is safe to bring into the classrooms for science projects and hands-on activities. A few teachers have benefited from this new program thus far. In the summer of 2017, Suncoast High School teacher Brett Stubbs worked on creating curricula around the materials available and a website will be created this semester where teachers can see the inventory, request materials, and download lesson plans. In the future, we hope to create a blog where teachers can post questions to which our scientists can respond. The new website allows for blog posting. The education, training, and outreach programs will pilot this technology this summer.

Scripps Research Florida Education Outreach Events this Fiscal Year

| Date | Event |
|---|---|
| October 22, 2019 | Microscopy Workshop at Jupiter High |
| October 30, 2019 | Sciences and Engineering Expo at Palm Beach State College |
| November 18, 2019 | STEAM Fest 2019 at PBSC |
| December 3, 2019 | Visit from Biotechnology Class to Scripps Research |
| December 12, 2019 | Palm Beach Regional Science & Engineering Fair |
| January 9-11, 2020 | Diversity Visitation Event for Research and Graduate Education(DiVERGE) |
| January 28, 2020 | PBC School District superintendent and staff visit to Scripps Research |
| January 29, 2020 | FAU PhD Program candidates visit to Scripps Research |
| February 8, 2020 | TLJMS Career Symposium at Inlet Grove HS |
| February 10, 2020 | Bethune School visit to Scripps Research |
| February 11, 2020 | BDB Education Showcase |
| February 13, 2020 | FAU PhD Program candidates visit to Scripps Research |
| February 20, 2020 | Atlantic HS school trip to Scripps Research |
| March 12, 2020 | Visit to Score Academy |
| April – May 2020 | Spring Series |

**Subsection (10) (g) No later than 3 years after occupancy of the permanent facility, the grantee shall establish a research program for middle and high school teachers.**

These programs were established in 2005. The permanent facility was occupied in 2009.

Scripps Florida Secondary School Teacher Workshops

Scripps Florida is directing greater efforts to address the needs of the classroom science teacher by establishing Teacher Workshops in basic science, math and laboratory skills. The Instructional Support Program for Innovative Research Education ("InSPIRE") programs offer direct interaction with the bioscience researchers at Scripps Florida and provide greater professional development opportunities for pre-service and in-service middle and high school science teachers in a supportive engaging environment. Portability of the lessons allows teachers to leverage the institute curriculum to their own classrooms during the course of the school year.

The program, which is supported by a grant from the National Science Foundation awarded to Dr. Brian Paegel, a faculty member in the Department of Chemistry, provides opportunities for teachers in the Palm Beach County to attend the workshops at Scripps Florida. Through its partnership with the school district, Scripps Florida emphasizes recruitment from schools with limited resources in rural and urban Palm Beach County, particularly in areas with large underrepresented and disadvantaged student populations. Dr. Paegel and his graduate students developed a new curriculum based on microscopy and image analysis applications. The last workshop was held in July 2017, and ten middle and high school teachers attended it. Future workshops will be announced on the Scripps Research website.

**Subsection (10) (h) No later than 18 months after occupancy of the permanent facility, the grantee shall establish a program for adjunct professors.**

Many current Scripps Florida faculty have received adjunct faculty appointments with the University of Florida, University of Miami and Florida Atlantic University. Such adjunct appointments are intended to provide a mechanism for graduate students enrolled in Florida research universities to collaborate with, to be co-mentored by, and to perform research in the laboratories of a Scripps Florida faculty member.

A mechanism has been established for faculty members at Florida institutions who have established collaborative research programs with Scripps Florida faculty to be appointed to an Adjunct Professor position. The process is initiated by a Scripps Florida faculty member who submits a nomination to his/her department chair. If the chair concurs, the chair submits the nomination to the Office of the President for review and approval.

**Subsection (10) (i) No later than 6 months after commissioning its high throughput technology, the grantee shall establish a program to allow open access for qualified science projects.**

Scripps Florida initiated the "Access to Technologies" program in January of 2006 to invite scientists from Florida universities and other academic research institutions to use state-of-the-art screening technologies at Scripps Florida's facilities in Jupiter for qualifying projects. An additional "Core" platform is now available at the Scripps Florida facility that combines basic research with advanced technology.

Access to Technologies is available to scientists who may not have these technologies available at their respective institutions and scientists are encouraged to utilize the web platform to learn more about these core technologies, ranging from an X-Ray Crystallography Facility, the Genomics and Proteomics

Cores, to the Nuclear Magnetic Resonance Core. To see a full list of different technologies used on the Florida and the California campuses, please visit:
https://www.scripps.edu/science-and-medicine/cores-and
services/://www.scripps.edu/research/resources/index.html

**Subsection (10) (j) Beginning June 2004, the grantee shall commence collaborative efforts with Florida public and private colleges and universities, and shall continue cooperative collaboration through the term of the agreement.**

On-going and new scientific collaborations between Scripps Florida scientists and colleagues from Florida colleges, universities, and local companies have continued. Also, please see the reply to Subsection (9) (f) which details these collaborations.

**Subsection (10) (k) Beginning 18 months after the grantee occupies the permanent facility, the grantee shall establish an annual seminar series featuring a review of the science work done by the grantee and its collaborators at the Florida facility.**

Collaborative seminars feature prominent Florida-based speakers from the academic, biotechnology or pharmaceutical communities and focus on topics within the broad fields of biomedical science, advanced technologies applied to biomedical research, drug discovery, and energy. External seminars are part of the institute series, inviting prominent researchers from national and international institutions to speak. Both serve as a major foundation for creating knowledge- and technology-sharing opportunities, team building, and collaborations among biomedical researchers between Scripps Florida, Florida, and other research and academic institutions and companies. The sessions are open to interested professionals within the Scripps Florida and Florida scientific communities. Many of the CA-based seminars are live-cast to the FL campus.

**Subsection (10) (l) Beginning June 2004, the grantee shall commence collaboration efforts with the Office of Tourism, Trade, and Economic Development (OTTED) by complying with reasonable requests for cooperation in economic development efforts in the biomed/biotech industry. No later than July 2004, the grantee shall designate a person who shall be charged with assisting in these collaborative efforts.**

Scripps Florida has designated Mr. Doug Bingham as its designee to assist the Department of Economic Opportunity ("DEO"), nee OTTED, regarding collaborative economic development efforts between Scripps and DEO.

If there are any questions about this annual report or the SFFC, please contact
Sara Misselhorn at saramisselhorn@yahoo.com or (561)889-1646.
Mailing Address: 130 Scripps Way, Suite B41. Jupiter, FL 33458.