**SCRIPPS FLORIDA ANNUAL REPORT FOR**
**THE YEAR ENDING JUNE 30, 2018**

## PART I: SCIENTIFIC ACHIEVEMENTS AND GRANT AWARDS

### A: SCIENTIFIC ACHIEVEMENTS

Scripps Florida 2018 Scientific Report
July 1, 2017 – October 4, 2018

**Part 1: New Faculty and Scientific Administration**

**Executive Appointments and Promotions**

December, 2017

- Eric Topol, MD, the founder and director of STSI, has been named executive vice president at TSRI. Topol will maintain his leadership responsibilities at STSI while taking on additional responsibilities, including overseeing communications at TSRI.

- Anna-Marie Rooney has been hired as Vice President of Communications to direct all marketing strategy and communications efforts for the Institute and its affiliates.

**The Scripps Research Institute Announces New Board Members**

LA JOLLA, CA & JUPITER, FL – May 16, 2018 – The Scripps Research Institute (TSRI), one of the world's largest, private, non-profit research organizations, today announced the appointments of two new members to its Board of Directors.

**TSRI Board of Director Appointees**

**John C. Martin**

Widely respected for his scientific and business leadership, Martin was named best CEO in 2015 by the investment research company Morningstar. As CEO of Gilead, a position he held for 20 years, Martin led the development of HIV and hepatitis therapeutics, overseeing the expansion of the company's drug portfolio to 24 marketed products. Through the Gilead Access Program, he oversaw the distribution of medicines for HIV/AIDS, viral hepatitis and visceral leishmaniasis, a parasitic disease, to developing countries.
"John is an outstanding scientist and a visionary business leader, and we are thrilled to have him on our Board," says Peter Schultz, president and CEO of The Scripps Research Institute. "He has long worked on the leading edge of antiviral research and he's made an extraordinary commitment to global health, providing patients around the world with access to life-saving medicines. That ideal aligns with our mission and he will be a tremendous asset as we intensify our focus on translational research."

Martin was Director of antiviral chemistry at Bristol-Myers-Squibb for six years prior to joining

Gilead in 1990 as Vice President of Research and Development. He became CEO in 1996 and then Executive Chairman in 2016. In 2018, he transitioned to his current role as Chair of Gilead's Board of Directors. Previously, he served on the Centers for Disease Control's Advisory Committee on HIV and STD Prevention and Treatment and was a member of the Presidential Advisory Council on HIV/AIDS. In 2008, he was inducted into the National Academy of Engineering.

Martin earned his bachelor's degree in chemical engineering from Purdue University, an MBA in marketing from Golden State University and a doctorate in organic chemistry from the University of Chicago.

**Sherry Lansing**

Among her current priorities as an advocate and philanthropist is the acceleration of cancer research. She is a co-founder of the Stand Up To Cancer initiative, which funds and facilitates patient-focused, collaborative cancer research.

"We are honored to have Sherry join our Board," says Peter Schultz, president and CEO of The Scripps Research Institute. "She brings leadership, focused energy and a passion for improving the lives of people affected by cancer. She recognizes the inroads we are making here and will be a great help in pursuing our mission of developing innovative medicines to improve human health."

Lansing became the first woman to head a major film studio when she took on the role of president at 20th Century Fox in 1980. In 1992, she became chair and CEO of Paramount Pictures, guiding the company to enormous creative and financial success. During her nearly 30-year career, Lansing led the production, marketing and distribution of more than 200 films, including Academy Award winners *Forrest Gump*, *Braveheart*, and *Titanic*.

After retiring from Paramount Pictures in 2005, she established the Sherry Lansing Foundation, dedicated to funding and raising awareness for cancer research, health, public education and encore career opportunities. She serves on the University of California Board of Regents and the Independent Citizens' Oversight Committee of the California Institute for Regenerative Medicine, as well as on the boards of the Carter Center, the Albert and Mary Lasker Foundation, the Entertainment Industry Foundation, the W.M. Keck Foundation, and the Pacific Council on International Policy.

Lansing graduated cum laude with a Bachelor of Science degree from Northwestern University.

**Current TSRI Board Members**

**John D. Diekman, Ph.D.**, Chairman of the Board, The Scripps Research Institute; Founding Partner of 5AM Ventures
**Peter G. Schultz, Ph.D.,** Vice Chair of the Board and President, The Scripps Research Institute; President, Calibr
**Paul Schimmel, Ph.D.**, Hahn Professor, Department of Molecular Medicine and Chemistry, The Scripps Research Institute
**Herb Boyer, Ph.D.**, Professor Emeritus of Biochemistry and Biophysics at the University of California, San Francisco
**Gerald Chan, Ph.D.**, Co-founded Morningside, a private equity and venture capital firm
**William R. Hearst III**, Chairman of the Board of Hearst Corporation, President of the charitable William Randolph Hearst Foundation, Affiliated Partner of Kleiner Perkins Caufield & Byers

(KPCB)
**Mark Edwards**, Founded Bioscience Advisors, Inc. (Biosci)
**Isy Goldwasser**, Co-Founder and Chief Executive Officer of Thync, Inc.
**Ge Li, Ph.D.**, Founder, Chairman and Chief Executive Officer of WuXi AppTec
**Christopher T. Walsh, Ph.D.**, Consulting Professor to the Stanford University Department of Chemistry
**Peter C. Farrell, Ph.D., D.Sc.,** Founder and Chairman, ResMed
**Claudia S. Luttrell,** President, The Skaggs Institute for Chemical Biology
**Mark Pearson,** Co-Founder, Vice Chairman of the Board, Drawbridge Realty Trust
**Bernard Saint-Donat,** President, Saint-Donat & Co.
**Ron Burkle**, **Founder,** Yucaipa Companies and Philanthropist
**Joel Marcus**, Chairman, Chief Executive Officer and Founder of Alexandria Real Estate Equities, Inc. (NYSE: ARE)

**The Scripps Research Institute welcomes renowned data scientist Amalio Telenti, M.D., Ph.D.**

LA JOLLA, CA – November 30, 2017 – The Scripps Research Institute (TSRI) today announced the appointment of Amalio Telenti, M.D., Ph.D. as Professor in the Department of Integrative Structural and Computational Biology. Telenti will also serve as Chief Data Scientist at the Scripps Translational Science Institute (STSI), providing leadership in developing and implementing large-scale analyses of medical, sensor, and genomic data.

Telenti is a leading data scientist and genomic researcher whose research foci include human genomics, as well as infectious disease research. He has an extensive background in directing scientific research and operations that spans academia and private sectors over three decades and multiple countries.

“Dr. Telenti is an important addition to TSRI’s world-class faculty roster,” said Peter Schultz, Ph.D., TSRI’s President and Chief Executive Officer. “He brings with him a wealth of experience in heading up genomics research and large-scale data analysis. We’re delighted to have him contribute his expertise towards the ground-breaking research being conducted at TSRI.”

Prior to joining TSRI, Telenti served as Chief Scientific Officer at Human Longevity, Inc. He also held faculty appointments at the University of Lausanne and University of Bern in Switzerland. As a clinician with over 25 years of experience, Telenti led the outpatient clinic at the University Hospital in Lausanne, specializing in infectious diseases and microbiology.

“Rapid technological innovation is enabling researchers to generate and delve deep into human data at an unprecedented scale,” said Telenti. “Translating this data into meaningful knowledge promises to transform medical care, diagnostics and drug development. I look forward to working alongside the exceptional scientists at TSRI to accelerate the usability of experimental data that is generated at the Institute."

STSI’s director, and TSRI’s Executive Vice President, Eric Topol, M.D., also welcomed Telenti. “We’re very excited to have Amalio join our team. His expertise in leading impactful big data biomedical projects will be invaluable to our efforts of a data-driven approach to individualizing medicine.”

**The Scripps Research Institute expands faculty with five new members**

LA JOLLA, CA & JUPITER, FL – July 11, 2018 - The Scripps Research Institute announced the addition of five new faculty members who bring diverse expertise to the Institute's bicoastal scientific research operations. The scientists, who include four women and one man, join an organization that the journal *Nature Index* recently ranked the #1 nonprofit research institution in the United States for producing "high quality research."

"We're very pleased to have these stellar scientists join our faculty," says Jamie Williamson, PhD, executive vice president of Research and Academic Affairs at the institute. "They're demonstrating incomparable talent across some of the most pioneering areas of current research."

The additions expand Scripps Research's faculty to nearly 220 members, split over two campuses. Two of the new researchers will be based at the institute's La Jolla, California campus:

Silke Paust, PhD, will join the Department of Immunology and Microbiology as an associate professor. Her work encompasses the development and testing of immunotherapies that elicit clinically relevant natural killer cell-mediated antiviral and antitumor immunity. She earned her doctoral degree in Immunology from Harvard University and most recently headed a laboratory at Baylor College of Medicine.

Lisa Racki, PhD, currently a postdoctoral researcher at the California Institute of Technology, will join the Integrative Structural and Computational Biology Department as an assistant professor. She studies how bacteria remodel their subcellular architecture to cope with starvation, which is important for survival in most environments including the human body in the context of chronic infections. She earned her doctoral degree in Biochemistry from the University of California, San Francisco.

The other three researchers from the incoming group will be based at Scripps Research's Jupiter, Florida campus:

Mia Huang, PhD, is currently a postdoctoral scholar at the University of California, San Diego. She will join the Department of Molecular Medicine as an assistant professor to continue studying chemical strategies to mimic and harness the nanoscale architecture and organization of proteoglycans for applications in regenerative medicine and musculoskeletal research. Huang earned her doctoral degree in Chemistry from New York University.

Michalina Janiszewska, PhD, most recently of the Dana-Farber Cancer Institute, Harvard Medical School, will join the Department of Molecular Medicine as an assistant professor. She is working on intratumor heterogeneity in breast and brain cancer, developing in vitro and in vivo methods to investigate relations between genetically distinct cancer cell populations. Janiszewska earned her doctoral degree in Cancer Biology from the University of Lausanne, Switzerland.

Chris Parker, PhD, who is currently a postdoctoral researcher at Scripps Research, will join the Department of Chemistry as an assistant professor. His work is centralized on the development and implementation of chemical proteomic methods to discover novel therapeutic targets. Parker earned his doctoral degree in Chemistry from Yale University.

"A key to our success here at Scripps Research is attracting talent from all around the world to join us in our efforts in basic research and discovery of new therapeutics," says Williamson. "With the addition of these researchers, we're building the foundation for our continued success."

**Scripps Research ranked top nonprofit scientific institute in United States**

*Scripps Research is the top stand-alone scientific institute in the United States for producing high-quality research, according to a recently released Nature Index ranking based on discoveries published in leading scientific journals.*

June 05, 2018: In addition to receiving the top overall US ranking, Scripps Research was ranked first in its class in the United States in both life sciences and chemistry research. Globally, Scripps Research ranked third in life sciences research and fourth in chemistry.

The new ranking, published June 7, follows a separate *Nature Index* ranking of Scripps Research last August as the most influential research institution overall in the world for its influence on innovation.

"These rankings speak to the culture of scientific excellence at Scripps Research and the commitment of our talented scientists to making seminal discoveries that simultaneously advance human knowledge and human health," says Jamie Williamson, PhD, Scripps Research's executive vice president of research and academic affairs. "We at Scripps know what a special place this is for discovery, but it's nice to have external validation."

The *Nature Index Annual Tables* show calendar year output in 68 high-quality journals for the last three years, and reveal the countries, institutions and companies that are leading the way in publishing high-quality global science. The *Nature Index* is compiled by Nature Research, part of Springer Nature.

This is the first year *Nature Index* has released tables ranking nonprofit organizations/non-governmental organizations (NPO/NGO), which include nonprofit scientific organizations, such as Scripps, that are not connected to a university or government agency.

Globally, Scripps Research was ranked fifth overall in the NPO/NGO category, behind several larger organizations in Germany and Russia, but the smallest of these is nearly ten times the size of Scripps Research. The rankings are not adjusted to account for the size of different institutions.

"Scripps Research swings well above its weight in terms of the quality and volume of its scientific output, which is made evident year after year by these rankings," says Williamson.

Scripps Research was the only organization in the NPO/NGO category to make the top 40 among institutions of all sizes and types in the United States. In the field of chemistry, among all institutions, Scripps ranked 13th in the United States, ahead of major research universities such as Yale, Columbia, Princeton and the University of California, Los Angeles.

Last August, Scripps Research was ranked the overall most influential research institution in the world by the *Nature Index* 2017 Innovation supplement. The ranking was based on the Normalized Lens Influence Metric, which measures the influence an institution's research has had on innovation by calculating the citations of its research articles in patents owned by third parties, rather than those owned by institutions themselves.

**Scripps Research Ranks No. 1 in Innovation Influence**

August 10, 2017: The Scripps Research Institute (TSRI) is the most influential research institution in the world, according to the Nature Index 2017 Innovation supplement, which sheds light on the impact of academic research on innovation. The ranking, released today by the journal Nature, analyzes data about research quality and the broad influence it has on inventions.

"This new ranking underscores the worldwide impact of TSRI scientists, who share a common goal of improving public health through scientific discovery, and, importantly, improving the way we make those discoveries," said Jamie Williamson, TSRI's Executive Vice President for Research and Academic Affairs. "We are proud to be recognized for the profound influence our science has had on other researchers and laboratories around the world."
The Normalized Lens Influence Metric used by the Nature Index measures the influence an institution's research has had on innovation by calculating the citations of its research articles in patents owned by third parties, rather than those owned by institutions themselves.

According to this metric, TSRI ranks number one, above other internationally renowned research institutes such as the Rockefeller University in New York, the Massachusetts Institute of Technology and Stanford University.

"This analysis comes at a time when following the transfer of scientific knowledge into industry and the economy is a growing priority for governments and research funding agencies, said David Swinbanks, founder of the Nature Index. "For them, the need to demonstrate that publicly funded science is being used for society's benefit is paramount,"

A key metric in this ranking is publications. More than 40 percent of all TSRI's natural science articles appear in the Nature Index. The average across the 200 institutions listed is 21.9 percent.

TSRI scientists are also active in developing their own innovations, with more than 1,000 patents and seven FDA approved drugs to their credit. Additionally, the Institute's recent alliance with the California Institute for Biomedical Research (Calibr) adds translational research to its capabilities, enabling a new bench-to-bedside model that will accelerate the translation of basic scientific discoveries into critically-needed new medicines for unmet medical needs.

**Graduate program at The Scripps Research Institute earns another top ten ranking**

LA JOLLA, CA & JUPITER, FL – Mar. 21, 2018 – The Skaggs Graduate School of Chemical and Biological Sciences at The Scripps Research Institute is ranked among the top ten in the nation according to a recent survey by *U.S. News & World Report*. This is the 19th year in a row that the program has earned top ten honors.

The Institute's Chemistry program ranks 6th in the nation and the Biological Sciences program ranks 10th, according to the survey, which was released March 20. For specialties within Chemistry, the graduate program tied for 2nd in Biochemistry (with Harvard) and earned a 5th place ranking in Organic Chemistry.

"These high rankings reflect an adherence to excellence by Scripps faculty, who originally conceived and developed the program, as well as the stellar students who join us here at the Institute as we explore the frontiers of science," says Phil Dawson, dean of Graduate and Postdoctoral Studies at the Institute.

According to Dawson, since its founding in 1989, the graduate program has placed over 100 alumni in faculty positions at major universities and colleges around the world. Hundreds more alumni, he says, have been placed in leadership roles in biotech and pharmaceutical companies.

Earlier this year, the Institute announced that one of its dedicated benefactors, the Skaggs family, was making a transformational lead gift toward an endowment campaign to establish fellowships for all students in the graduate program. In honor of that gift, the program was renamed the Skaggs Graduate School of Chemical and Biological Sciences. The Institute itself was ranked #1 in the world last year by *Nature Index* for its "influence on innovation."

**Part 2: Grant Awards and Licensing Agreements**

**New Exploratory Grant Will Help Scripps Florida Scientists Advance Treatment Development**

JUPITER, FL – August 24, 2017 - Scientists from the Florida campus of The Scripps Research Institute have been awarded nearly $1 million from the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, to develop a genetically engineered animal model of a debilitating inherited disease that could accelerate the development of potential treatments.

Joseph Kissil, a TSRI associate professor in the Department of Molecular Medicine, is the principal investigator for the three-year grant. This is a phased award; if certain benchmarks are met, the grant is extended for a third year.

Kissil has been studying Neurofibromatosis Type 2 (NF2) for a number of years. The disease is caused by mutations in the anti-tumor gene *NF2*, which leads to tumors of the auditory nerve that connects the inner ear to the brain and causes severe hearing loss and impaired balance and walking. A majority of patients develop additional tumors throughout the nervous system, which can lead to fluid buildup in the brain and seizures.

While knowledge of the molecular mechanisms underlying the disease has improved significantly over the past two decades, there are still no effective treatments. Current options are non-curative and include surgery, radiation therapy, as well as temporary interventions for symptom control.

"Clearly, there is an urgent need to develop better options for these patients," Kissil said. "One of the main obstacles is the lack of animal models that can be used in pre-clinical testing of drug candidates. This grant will help us develop a genetically engineered animal model of the disease that accurately portrays the biology of tumor development in patients – and that can be used to evaluate drug candidate efficacy."

In 2013, Kissil and his colleagues identified a new drug candidate to treat NF2. The compound — known as FRAX97—slowed the proliferation and progression of tumor cells in some preliminary animal models of the disease. Originally developed for neurodegenerative disease, the compound targets a protein family known as p21-activated kinases or PAKs. These kinases (enzymes that add a phosphate group to other proteins and change their function) play a critical role in the development of NF2.

"While the models that we used then offered a good approximation, they were just that – an approximation," Kissil said. "There's still a great need for models that more closely reflect what happens in patients and that the new model we're working on does just that."

The number of the grant is1R21NS099417-01A1

**Institute Researchers Join National Digital Health Informatics Collaborative**

JUPITER, FL – October 02, 2017 - Informatics experts at The Scripps Research Institute (TSRI) have been awarded close to $3 million as part of a five-year cooperative agreement to launch the National Center for Data to Health (CD2H).

The collaborative initiative is part of a $25 million grant funded by the National Center for Advancing Translational Science (NCATS), which is part of the National Institutes of Health. Oregon Health & Science University (OHSU) is the prime recipient of the grant.

The award supports efforts to integrate informatics activities across the Clinical and Translational Science Award (CTSA) program, a network of more than 50 medical research institutions, and to provide collaborative clinical and translational research infrastructure.

"Advances in data science are transforming how we conduct biomedical research in both translational and clinical fields. The key is to deliver relevant and up-to-date, ideally real-time, information to researchers in a more efficient way, given the sheer amount of data being produced every day," describes Chunlei Wu, Ph.D., associate professor of integrative structural and computational biology at TSRI and the site principal investigator (PI) for TSRI on this grant.
The newly created center will be led by researchers from OHSU, Northwestern University, University of Washington, Johns Hopkins University School of Medicine, and Sage Bionetworks, together with TSRI, Washington University in St. Louis, the University of Iowa and The Jackson Laboratory.

"The goal is to unlock the amazing wealth of technologies and innovation located within each individual CTSA member institution, and to create cohesive communities of practice founded on the fundamental premise that team science, data sharing, and collaborative innovation can advance patient care," describes Melissa Haendel, Ph.D., associate professor of OHSU and the leading PI on this grant.

The CD2H will have several priorities to support a vibrant and evolving informatics ecosystem across the CTSA consortium. These include support and enhancement of a collaborative informatics community; promotion of software standards for interoperability; growth of collaborative innovation across informatics tools, methods, and processes; data science education for CTSA program researchers; and development of novel methods and tools for the evaluation of the impact of these activities to enhance health care through data and informatics.

Wu and his team at TSRI will be tasked with building the high-performance and scalable data access infrastructure and defining community best practice for data processing and software implementations. Wu will also work together with Ali Torkamani, Ph.D., associate professor of integrative structural and computational biology at TSRI and director of genomics of the Scripps

Translational Science Institute (STSI), to ensure the data produced at local CTSA hubs are accessible in a coherent way by other CTSA hubs, as well as by the general research community.
"As a CTSA hub that has been emphasizing genomic and digital sensor bioinformatics, we are thrilled to help pave the data-to-health path with OHSU and a remarkable network of collaborators," says Eric Topol, M.D., professor of molecular medicine at TSRI, who also directs STSI, which is supported in part by NCATS and is a member of the CTSA consortium (Grant UL1 TR001114).

The CTSA Program National Center for Data to Health is supported by the National Center for Advancing Translational Sciences at the National Institutes of Health (Grant U24TR002306).

**Scripps Florida Scientists Share $9 Million Grant to Develop Therapies that Target the Aging Process**

JUPITER, FL – October 16, 2017 - Scientists from the Florida campus of The Scripps Research Institute (TSRI) and Albert Einstein College of Medicine will share in a $9 million grant from the National Institute on Aging, part of the National Institutes of Health, to study how individual genetic differences may form the basis for new therapeutic approaches that target the aging process itself rather than focusing on the treatment of individual diseases.
Paul Robbins, TSRI professor in the Department of Molecular Medicine and Director of the TSRI Center on Aging and Jan Vijg, professor and chair of genetics of Albert Einstein College of Medicine will lead the study. Approximately half the funding will go to TSRI.

The new five-year study focuses on determining the genetic differences between those people who have aged well and those who have not – differences that can be used to pinpoint new therapeutic targets that could delay or possible even reverse many age-related diseases.

"We call them 'natural longevity mutants'—human centenarians and super-centenarians who have managed to ward off the diseases that normally begin to plague everyone at middle age," Robbins said. "They have changes in their genetic makeup that allow them to live to a ripe old age. If we can validate these variants in animal models and test them to see if they live longer, we can begin to develop drugs that increase healthspan."

It is estimated that in the next 20 years, the number of individuals in the United States over the age of 65 will double, reaching more than 70 million individuals, so the need to identify new therapeutic strategies to extend healthspan—healthy aging—is increasingly urgent.

"It's a new and intriguing concept: genome to drug," Robbins said, "These natural occurring human genetic variants are an ideal starting point for our genome-to-drug approach."

The scientists have already identified multiple genes and pathways that potentially can be manipulated in humans to delay aging through drug treatment—and slow the consequences of its accompanying diseases.

They already have the complete genomes of 660 of these 'longevity mutants,' and hope to have 1,500 finished by the end of the first year of the research, Robbins said.

The new studies will make extensive use of a mouse model of accelerated aging created in the laboratory of TSRI Associate Professor Laura Niedernhofer—not only to validate these rare variants but to test and validate compounds that target them.

"We've already used the mouse model of accelerated aging to identify some possible targets and pathways for extending healthy aging," Niedernhofer said. "In fact, several different senolytic drugs and young stem cells are already able to extend healthspan in our models."

In a recently published study in the journal *Nature Communications*, Robbins and Niedernhofer identified a new class of drugs that target senescent cells—cells that have stopped replicating because of chromosome damage. As we get older, senescent cells accumulate, becoming a major contributor to age-related diseases. These new compounds have the potential to significantly delay the onset of several age-related symptoms and extend healthy aging.

The number of the grant is 1U19AG056278-01.

**Skaggs family makes "transformational" lead gift toward The Scripps Research Institute's Graduate Program endowment**

LA JOLLA, CA & JUPITER, FL - January 17, 2018 –The Scripps Research Institute (TSRI) announced that the Skaggs family has made a lead gift through their foundations toward TSRI's $100 million campaign to establish fellowships for all students in its Graduate Program. In recognition of this gift, the program will be renamed the Skaggs Graduate School of Chemical and Biological Sciences.

"This transformational gift by the Skaggs family to our Graduate Program is a vote of confidence in our continuing strategy of building excellence in education and research, which are inextricably linked," says Peter Schultz, TSRI president. "It recognizes the outstanding scientific discoveries that have been and will continue to be produced by the students of TSRI's top ten program." *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 18 straight years. According to Schultz, since its founding in 1989, the Graduate Program has placed over 100 alumni in faculty positions at major universities and colleges around the world. Hundreds more alumni, he says, have been placed in leadership roles in biotech and pharmaceutical companies.

The Skaggs family's gift will make it possible for individual supporters of the Graduate Program to donate $500,000 that will then be supplemented by an additional $500,000 from The ALSAM Foundation and the Skaggs Foundation for Research to create a $1 million endowment for an individual named student fellowship. Phil Dawson, the dean of Graduate and Postdoctoral Studies, emphasizes that members of TSRI's faculty and Board of Directors have made personal donations to the campaign, totaling more than $10 million to date. "We really value our students here at Scripps," Dawson says. "In fact, our Graduate Program was originally conceived and developed by Scripps faculty. Training the next generation of creative scientists is central to our identity."

The Skaggs family has a long history of supporting biomedical research at TSRI, helping to build it into an institution that *Nature Index* ranked #1 in the world for its "influence on innovation." "This latest naming gift continues the decades-long legacy of support of TSRI by the Skaggs family that

propelled us to the forefront of technological innovation and transformational discoveries," says Jamie Williamson, executive vice president.

Beginning in the 1980s, food and drugstore pioneer L.S. "Sam" Skaggs and his wife, Aline, began making numerous financial gifts to the Institute, including underwriting the construction of The Aline W. & L.S. Skaggs Nuclear Magnetic Resonance Spectroscopy Center. In 1996, their commitment of $100 million—at the time, one of the largest gifts ever to higher education—created The Skaggs Institute for Chemical Biology. There, according to an Institute news release, an interdisciplinary team of scientists was created to "realize their full potential at the vital intersection of chemistry and biology," an effort that led to several drugs.

Although Sam passed away in 2013, followed by Aline in 2015, their strong philanthropic interest in scientific research and education is maintained by their children. Their son Mark Skaggs has served on TSRI's Board of Directors and their daughter Claudia Skaggs Luttrell currently plays an active role on the Board. In addition to her family's gift to the endowment campaign, Luttrell made a personal donation, as did her adult children, Dallas and Jennifer.

Jeff Kelly, the chair of Chemistry at TSRI, was one of the first faculty members to donate to the Graduate Program endowment campaign. His gift was doubled by the Skaggs' foundations. He calls the Skaggs family's philanthropic commitment a call to action. "For three generations—from Sam and Aline to their children and now their grandchildren—the Skaggs family has been generously supporting scientific research, higher education and drug discovery at TSRI. This latest gift toward ensuring that students in our Graduate Program receive a top-tier education will have a huge impact on our science for years to come. I couldn't be more grateful to Claudia and Mark, and their siblings, Don and Susie."

The Institute is planning to stage an event in late spring to celebrate the generous gift and the renaming of the program.

**Cancer researchers receive more than $2 million to eradicate common form of leukemia**

JUPITER, FL – April 10, 2018 - Christoph Rader, PhD, associate professor at the Florida campus of The Scripps Research Institute, has been awarded a $2.875 million, five-year grant from the National Cancer Institute to develop unique antibody-drug conjugates engineered to eradicate one of the most common forms of leukemia, chronic lymphocytic leukemia (CLL).

"We want to attack the cancer without harming healthy cells and tissues," Rader says. "To do this, we attach a highly potent drug to an antibody and then use the antibody to lead the drug payload to the cellular target."

Doctors diagnose more than 20,000 people a year in the United States with chronic lymphocytic leukemia. The blood cancer originates in a type of white blood cells called lymphocytes, born in bone marrow. As the condition worsens over time, the cancerous cells accumulate, crowding out healthy blood cells. When they move into the blood stream, the malignant cells can spread to other organs and disrupt their healthy function. The illness can cause fatigue, fever and infections, swelling of the lymph nodes and weight loss. More than 4,500 people die each year of CLL in the United States.

The central challenge in fighting all cancers is attacking the malignancy without hurting other parts of the body. Antibodies, the immune system's adaptable targeting system, recognize and bind to specific threats. Using them to attack cancer requires designing ways to attach drug payloads, and then identifying ideal points of attack. Rader's team discovered a binding site on the surface of CLL lymphocytes, called FCMR, which pulls antibodies into the cells in a matter of minutes.

"This particular target is selectively expressed in CLL," Rader says, which means antibodies that bind to the cancer won't attack other, healthy cells.

Attaching the drug payload to the antibody requires a third element, a linking molecule. Working with Scripps Research chemists, including Assistant Professor Hans Renata, PhD, and Professor Emeritus William Roush, PhD, Rader's group has devised several approaches that perform well.

"This draws on the unique interface of biology and chemistry we have here at Scripps Florida. We are creating new molecules with precise designs that are now able to selectively target CLL cells," Rader says. "There is a dire need for the development of new, effective and safe therapies against chronic lymphocytic leukemia."

The grant is number 2R01CA174844-04.

**Autism research to advance with $3.6 million NIH grant to Scripps Florida team**

JUPITER, FL – May 22, 2018 - Gavin Rumbaugh, PhD, of The Scripps Research Institute's Florida campus, will lead a 5-year, $3.6 million grant from the National Institute of Mental Health to continue studies of abnormal brain circuitry in autism.

The grant builds upon previous work from the Rumbaugh lab that uncovered a sensitive period in brain development during which an autism and intellectual disability risk gene called *Syngap1* must function properly to promote assembly of circuitry needed for healthy social and cognitive development.

With the new funding, the team plans to focus on how this *Syngap1*sensitive period regulates developmental processes that link sensory processing to learning, and how harmful *Syngap1* mutations may lead to autism-associated behavioral changes through sensory dysfunction.

Sensory processing impairments are nearly universal in children with neurodevelopmental disorders, such as autism and intellectual disability. However, it is unclear how and where in the brain altered sensory processing impairs learning and drives altered behaviors in these disorders.

"Our *Syngap1* animal models are an excellent way to investigate the direct neurobiological links between autism-associated sensory processing impairments and behavioral changes also seen in these children," Rumbaugh says. "Understanding how these processes are linked is critical to identifying the brain circuits that are not functioning properly and contributing to the cause of these disorders."

The work will be performed in collaboration with Scripps Research Associate Professor Courtney Miller, PhD, and Jason Christie, PhD, a researcher at the Max Planck Florida Institute for Neuroscience. The proposed studies require the real-time measurement of brain activity in *Syngap1* mice undergoing behavioral training in a variety of sensory detection tasks. Miller's

expertise in developing complex rodent behavioral paradigms, and Christie's successful adoption of emerging tools to measure brain activity in behaving animals, are critical to the project, Rumbaugh says.

"This project reflects the growing need for researchers with diverse expertise to collaborate in order to solve important problems in neuroscience," Rumbaugh says.

The number of the grant is R01 MH096847.

**Quest for safer pain-medications garners $3.6 million, five-year grant**

JUPITER, FL – August 17, 2018 - Researchers aim to control pain without the risk of addiction. The National Institute on Drug Abuse, part of the National Institutes of Health, has awarded a five-year, $3.68 million grant to two Scripps Research scientists, Laura Bohn, PhD, and Thomas Bannister, PhD, to advance their work developing safer pain medications.

Previously, Bohn and Bannister, based in Jupiter, Florida, had developed new compounds that separate the powerful pain-relieving benefit of opioids from the life-threatening side-effect of decreased breathing rate and lower blood-oxygen levels. The new round of funding enables the team to further improve these compounds while also evaluating the extent to which other common opioid side effects, including constipation, drug tolerance, and especially addiction risk, are inherently altered in these new compounds, with an eye toward further widening the safety margins.

"We want to determine if these compounds produce drug preference, which is a sign of abuse potential, and to make new compounds that have built-in abuse deterrence — to control pain without the risk of addiction," Bohn says.

People who experience severe pain from cancer, car accidents, surgeries, burns and other traumas frequently require powerful pain relievers, sometimes for sustained periods. Because tolerance develops over time, their physicians often must increase dosage to maintain pain relief, raising the risk of overdose and addiction. New pain medications that diminish pain, minimize risk of overdose and other side effects, and also limit abuse potential, are sorely needed, Bohn says.

An expert in a cell-signaling system called G-protein-coupled receptors, Bohn worked many years with Bannister, a medicinal chemist, to develop compounds that activate a receptor called the mu opioid receptor, which relieves pain, without likewise activating the beta-arrest in pathway, associated with the harmful effects of pain killers. They published their findings in the journal *Cell* last year.

"Many leaders in the field of pain research have steered away from targeting the mu opioid receptor due to severe side-effects. Knowing that several of these effects can, in fact, be avoided is a finding that could offer hope to people who need effective but safe pain relief," Bannister says.

*The grant number is 2R01DA033073-06.*

**Part 3: Scientific Accomplishments**

**New Study Demonstrates Importance of Studying Sleep and Eating in Tandem**

JUPITER, FL. – October 12, 2017 - A new study from scientists on the Florida campus of The Scripps Research Institute (TSRI) offers important insights into possible links between sleep and hunger—and the benefits of studying the two in tandem. A related paper from the same lab is providing researchers an accessible tool for pursuing further investigations involving multiple fruit fly behaviors.

While many humans enjoy a daily caffeine fix, scientists have found that caffeine repels *Drosophila melanogaster*—a species of fruit fly often used as a model for studying human conditions and genetics. Scientists believe that plants produce the caffeine molecule as a defense mechanism to prevent organisms such as fruit flies from eating them. Regardless of the cause of the fly's aversion, caffeine does seem to negatively impact their sleep, much like it does in humans.

Caffeine is known to stave off sleep in humans through pharmacological effects on the adenosine receptor. Nonetheless, many studies in mammals have shown genetic differences in responses to caffeine. Interestingly, caffeine apparently can prevent sleep in fruit flies despite the fact that it doesn't act through their adenosine receptor.

Erin Keebaugh, Ph.D., a postdoctoral researcher in Associate Professor William Ja's Laboratory at TSRI, suspected that the systems responsible for caffeine's impact on fly (and maybe human) sleep patterns are more complex than a single caffeine and receptor interaction.

In her study, published in the journal *Sleep* on October 3, 2017, her team gave groups of flies varying levels of dietary caffeine. They then measured how much the flies slept in the following 24 hours while on those diets. They also studied whether varying levels of caffeine impacted the insects' feeding behavior by measuring how much they ate over the same 24-hour period.

Interestingly, the team found that sleep loss couldn't be explained by caffeine intake alone. Instead, they believe that the sleep loss was mediated by changes in the animal's feeding behavior. "There could still be a pharmacological effect, but there's definitely dietary inputs to that," said Keebaugh.

The study reinforced the idea that the processes of sleep and eating need to be studied together, explained the scientists, especially as a growing number of researchers investigate the relationship between sleep and metabolic disorders. Further studies into this relationship could lead to the development of therapies that treat disorders such as obesity and diabetes.

### A Closer Look at Fly Behavior

To that end, another member of the Ja Laboratory, Graduate Student Keith Murphy, has developed a new open-source, customizable technique for jointly studying multiple fly behaviors. Many studies designed to understand the interactions between multiple fly behaviors require researchers to measure each behavior separately; for example, one study measures how much the flies eat while a second study measures how much they sleep, and then the data are combined and compared. With Murphy's device, the Activity Recording CAFE (ARC), researchers could measure both behaviors simultaneously, giving the researchers a cleaner, simpler strategy to investigate previously convoluted questions.

Using the ARC protocol, as described in a paper recently published in *Nature Protocols*, anyone with access to a 3D printer can print the chamber and set it up in two hours or less to collect fly data. The chamber is hooked up to a computer that continuously tracks both the amount of food that a fly consumes and its position in the chamber, which can tell a researcher whether or not it's sleeping.

Though the protocol is specifically designed for studying sleep and feeding behaviors, Murphy emphasized that the ARC could be customized to study a variety of behaviors in flies. Researchers could program the machine vision program on the computer to apply optogenetic controls tied to certain behaviors, deliver vibrations or cause the fly's food to move to assess memory, motivation and other behaviors.

"We're hoping that this paper creates a community around the tool and people come up with new uses," said Murphy. "If others get on board, this thing could change what a small lab can do."

In addition to Keebaugh, other authors of the study in *Sleep*, titled "Nutrition influences caffeine-mediated sleep loss in *Drosophila*," were Jin Hong Park, Chenchen Su, Ryuichi Yamada and William Ja of TSRI. The research was supported by the National Institutes of Health (grant R01AG045036).

In addition to Murphy, other authors of the *Nature Protocols* paper, titled "Simultaneous measurement of sleep and feeding in individual *Drosophila*," were Jin Hong Park and William Ja of TSRI and Robert Huber of Bowling Green State University. The research was supported by the National Institutes of Health (grant R21DK092735).

**Scripps Florida Scientists Unveil 'Roadmap' to Aid Osteoporosis Treatment Development**

JUPITER, FL – October 13, 2017 - Using advanced mass spectrometry technology, scientists from the Florida campus of The Scripps Research Institute (TSRI) have developed a molecular model that may provide a new framework for improving the design of osteoporosis treatments.
"Because of our aging population, these kinds of therapeutics are in great demand," said study leader Patrick R. Griffin, co-chair of the TSRI Department of Molecular Medicine. The research was published today in the journal *Nature Communications*.

Using a technology known as HDX, which the Griffin lab has propelled into mainstream protein analysis, the scientists delivered the first dynamic snapshots of a prime target for osteoporosis treatments: a receptor that regulates calcium levels to maintain healthy bones.

The use of current drugs that target this receptor—called vitamin D receptor agonists—is limited because use can result in hypercalcemia, a condition that can weaken bones and even cause kidney stones, due to too much calcium in the bloodstream.

To address this problem, scientists need a clearer picture of the structure of the vitamin D receptor. The vitamin D receptor complex regulates bone mineralization by controlling a gene known as BGLAP that is the target of 1α, 25-dihydroxyvitamin $D_3$ (1,25D3), the active hormonal version of vitamin D. Unfortunately, increased levels of 1,25D3 also activate a calcium-regulating gene called TRPV6, which leads to hypercalcemia.

Griffin and his colleagues hope to eliminate this threat by developing 1,25D3 analogs (known as dissociated vitamin D receptor ligands or VDRMs) that differentially target BGLAP genes, while avoiding TRPV6.

"The idea is that if we could fingerprint how these various ligands interact with the vitamin D receptor, we could provide a kind of roadmap to help develop those that only trigger the non-hypercalcemia gene," Griffin said.

Until now, developing more selective compounds has been hampered by the fact that no one understood the structural mechanism that makes them work.

"This study shows it's possible to develop a drug that can alter certain aspects of the complex to avoid problematic activation of TRPV6 —and the study points to novel ways to design potential therapeutics to treat osteoporosis safely and more effectively," Griffin noted.

Griffin and his colleagues performed a detailed comparative biophysical study on hundreds of compounds, all with distinct chemical structures.

"Our results provide snapshots of distinct conformational ensembles of the receptor, which allows it to adopt different orientations depending on compound structure, DNA and co-activator binding," said TSRI Research Associate Jie Zheng, the first author of the study. "This study shows the molecular mechanism of a selective vitamin D receptor modulator versus agonists and how they drive different interactions with co-regulators when associated with sequence-specific DNAs."

The scientists used hydrogen-deuterium exchange (HDX) mass spectrometry, a high-precision, high-sensitivity mapping technique that has proven to be a robust method to probe protein conformational or shape changing dynamics within the context of ligand and protein/protein interactions.

HDX can show the specific regions of the protein complex that are altered on interaction with specific ligands, in this case the vitamin D receptor complex, information which can be used to infer structural changes that are the result of a specific interaction.

In addition to Griffin and Zheng, other authors of the study, "HDX Reveals the Conformational Dynamics of DNA Sequence Specific VDR Co-Activator Interactions," are Mi Ra Chang,Bruce D. Pascal, Scott J. Novick, and Ruben D Garcia-Ordonez of TSRI; and Jeffrey Dodge, Ryan E. Stites, Yong Wang, Keith R Stayrook, and Michael J. Chalmers of Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN; and John B. Bruning of The University of Adelaide, Adelaide, South Australia.

**New Research Opens the Door to 'Functional Cure' for HIV**

JUPITER, FL – October 17, 2017 - In findings that open the door to a completely different approach to curing HIV infections, scientists from the Florida campus of The Scripps Research Institute (TSRI) have for the first time shown that a novel compound effectively suppresses production of the virus in chronically infected cells, and prevents viral rebound, even when those infected cells are subjected to vigorous stimulation.

The study, led by TSRI Associate Professor Susana Valente, was published online Oct. 17 before print in the journal *Cell Reports*.

"No other anti-retroviral used in the clinic today is able to completely suppress viral production in infected cells *in vivo*," Valente said. "When combining this drug with the standard cocktail of anti-retrovirals used to suppress infection in humanized mouse models of HIV-1 infection, our study found a drastic reduction in virus RNA present—it is really the proof-of-concept for a 'functional cure.'"

Valente, a pioneer in this new approach, calls it "Block-and-Lock"—the approach blocks reactivation of the virus in cells, even during treatment interruptions, and locks HIV into durable state of latency.

Valente and her colleagues use a derivative of a natural compound called didehydro-Cortistatin A (dCA), which blocks replication in HIV-infected cells by inhibiting the viral transcriptional activator, called Tat, halting viral production, reactivation and replenishment of the latent viral reservoir.

"Combining dCA with anti-retroviral therapy accelerates HIV-1 suppression and prevents viral rebound after treatment interruption, even during strong cellular activation," Valente said. "It's important to note that our study uses the maximum tolerable dose of the drug—with virtually no side effects."

The scientists studied the combination therapy in a mouse model of HIV latency and persistence. Once the combined treatment regimen was halted, viral rebound was delayed up to 19 days, compared with just seven days in mouse models receiving only anti-retroviral treatment.

"This demonstrates the potential of 'block-and-lock' strategies," said TSRI Research Associate Cari F. Kessing, co-first author of the study. "This study shows that a 'functional cure' approach can succeed in reducing residual virus in the blood during anti-retroviral treatment and limiting viral rebound during treatment interruption."

"In half of the dCA treated mice, the virus was undetectable for 16 days after all treatment was halted," said the University of North Carolina's Christopher Nixon, another first author.

"We blocked Tat, and the cell's machinery did the rest," said TSRI Research Associate Chuan Li, a coauthor of the study. "The result was that the HIV promoter becomes repressed."

Valente pointed out that the animal models were exposed to just a single month of treatment. "That's a relatively short period of time," she said. "We think longer treatments will result in longer, or even permanent, rebound delays. The question is how long? We're studying that now."

Because any viral rebound of HIV comes with a host of adverse effects, Valente noted, blocking that rebound would automatically reduce those effects.

"This is the only class of drugs that stops infected cells from making viruses outright," said Valente. "All current antivirals work later in the viral lifecycle, so only a HIV transcriptional inhibitor like dCA can stop the side effects of low-level virus production."

In addition to Valente, Kessing, Li and Nixon, other authors of the study, "*In Vivo* Suppression Of HIV Rebound By Didehydro-1 Cortistatin A, A 'Block-And-Lock' Strategy For HIV-1 Treatment," are Guillaume Mousseau and Mohammad Fallahi of TSRI; Perry M. Tsai, Phong T. Ho, Jenna B. Honeycutt and J. Victor Garcia of the University of North Carolina; and Hiroshi Takata and Lydie Trautmann of Walter Reed Army Institute of Research and the Henry M. Jackson Foundation for the Advancement of Military Medicine.

The study was supported by the National Institutes of Health (grants R01AI097012, R01AI118432, MH108179 and AI-111899), The Campbell Foundation and CARE, a Martin Delaney Collaboratory (1UM1AI126619).

**New Study: 'Double Decker' Antibody Technology Fights Cancer**

JUPITER, FL – October 25, 2017 - Scientists from the Florida campus of The Scripps Research Institute (TSRI) have created a new class of antibody-drug conjugates (ADCs), using a versatile "double decker" technology that ties antibodies and a drug together to produce highly potent pharmaceuticals for cancer therapy.
The new ADC technology advances a class of pharmaceuticals that use antibodies to selectively deliver drugs to cancer cells without harming healthy cells and tissues.

The study, published online this week in the journal *Nature Communications*, was led by TSRI Associate Professor Christoph Rader and TSRI Professor William R. Roush.

"Our new ADCs are built something like a double-decker bus," Rader said. "The upper deck is a targeting antibody that locks onto a cancer cell, while the lower deck is a catalytic antibody that carries the drug. This is yet another exciting application of an incredibly versatile class of catalytic antibodies originally developed by TSRI's Carlos F. Barbas III and Richard A. Lerner in the 1990s."

The name for this new technology is dual variable domain antibody-drug conjugates or DVD-ADCs.

Antibodies are large immune system proteins that recognize unique molecular markers on cancer cells called tumor antigens. On their own, antibodies are usually not potent enough to eradicate cancer. However, their high specificity for tumor antigens makes them ideal vehicles for drug delivery straight to cancer cells.

The new DVD-ADCs were used against HER2-driven breast cancer, as well as multiple myeloma and non-Hodgkin lymphoma, and the technology proved highly effective against all three types of cancers in both cell and animal model studies.

Not only is the new technology highly efficient, Rader explained, but it uses a modular assembly so it's relatively simple to apply to different cancers and possibly to other diseases.

"The advantage is we can produce ADCs at a fast rate in a single step," said Graduate Student Alex Nanna, first author of the study. "The DVD-ADC format brings everything together in a very efficient way."

The DVD-ADCs take advantage of an unusually reactive amino acid residue, a natural lysine of the catalytic antibody. "We can tie drugs with high precision and stability to this residue and, what's more, we can use it to monitor attachment because the antibody loses its catalytic activity when the drug attaches to the lysine. It's a very clean and unique way to confirm successful ADC formation," Rader said.

The technology also eliminates the need to purify the antibody during initial production, postponing that process until the ADC is assembled. "From a manufacturing point of view, this is a substantial advantage." Rader said.

There are currently only four FDA-approved ADCs for cancer therapy, of which two have been added this year alone.

"There is new excitement in this field," Rader said. "One ADC was recently approved in acute lymphoblastic leukemia and there's a rich clinical and preclinical pipeline."

In addition to Rader, Roush and Nanna, other authors of the study, "Harnessing a catalytic lysine residue for the one-step preparation of homogeneous antibody-drug conjugates," include TSRI's Xiuling Li (now with Pfizer), Even Walseng (now with the National Cancer Institute), Lee Pedzisa and Rebecca S. Goydel; and David Hymel and Terrence R. Burke Jr. of the National Cancer Institute.

The study was supported by the National Institutes of Health (grant U01 CA174844), the Klorfine Foundation, the Holm Charitable Trust, the Celia Lipton Farris and Victor W. Farris Foundation and the Division of Medicinal Chemistry of the American Chemical Society.

**New Painkillers Reduce Overdose Risk**

JUPITER, FL – November 16, 2017 - Scientists on the Florida campus of The Scripps Research Institute (TSRI) have developed new opioid pain relievers that reduce pain on par with morphine but do not slow or stop breathing—the cause of opiate overdose.

The research, published today in the journal *Cell*, describes a method for making safer opioid painkillers. According to the U.S. Centers for Disease Control and Prevention, 91 Americans die every day from opioid overdoses—deaths caused when opiates like oxycontin, heroin and fentanyl slow and eventually stop a person's breathing.

Study leader TSRI Professor Laura M. Bohn, Ph.D., said the research shows that a range of compounds can deliver pain-blocking potency without affecting respiration.

The study builds on two decades of research by Bohn and her colleagues, who long questioned whether the painkilling pathway, called the G protein pathway, could be unlinked from the breathing suppression pathway, called the beta-arrestin pathway.

"One of the questions we had was how good we can get at separating out the pathways, and how much separation do we need to see analgesia without respiratory suppression," Bohn said.

For the study, the Bohn worked closely with TSRI chemist Thomas Bannister, Ph.D, to develope new potential drug molecules; they then tweaked their chemical structures to systematically vary the "bias" between the two pathways—G protein signaling and beta-arrestin recruitment. The group developed more than 500 compounds in the past six years, and they found more than 60 that showed bias between signaling assays. They then selected six compounds to represent a wide range in the degree of bias (from those that preferred barrestin2 recruitment to those that almost exclusively preferred G protein signaling) and determined their overall potency for inducing analgesia and respiratory suppression in mouse models.

The researchers found that the new compounds could indeed enter the brain—and all of the compounds were as potent, if not more so, than morphine. The compounds that were less able to promote barrestin2 associations in cells were also less likely to induce respiratory suppression in mice.

In contrast, the painkiller fentanyl was shown to prefer receptor-barrestin2 associations and also had a more narrow safety margin. In short, the fentanyl dose needed to alleviate the perception of pain was

closer to the dose that suppressed breathing, which may be why fentanyl is more likely to trigger respiratory suppression at low doses. Fentanyl is a powerful pain killer, but one with a narrow therapeutic window and a history of overdoses. While this issue requires more research, “this at least brings into question whether this may be part of the reason,” Bohn said.

Bohn explained that separating the receptor's ability to engage in the two pathways can provide a way to separate desired drug effects from side effects.

“I think what we have done here is shown that bias isn’t all or none—that there is a spectrum.” That suggests an opportunity to expand the “therapeutic window,” or the range of doses at which a drug may be administered safely, she said.

The results announced today are the culmination of nearly six years of work by TSRI scientists including Cullen Schmid, Ph.D., Nicole Kennedy, Ph.D., and Michael Cameron, Ph.D.; as well as former members of the research lab: Jenny Morgenweck, Ph.D., Zhizhou Yue, Ph.D., Kim Lovell, Ph.D. and Nicolette Ross, Ph.D. The work was funded by the National Institute on Drug Abuse of the National Institutes of Health (grants R01 DA033073 and R01 DA038694).

**To forget or to remember? Memory depends on subtle brain signals, scientists find**

JUPITER, FL – November 21, 2017 - The fragrance of hot pumpkin pie can bring back pleasant memories of holidays past, while the scent of an antiseptic hospital room may cause a shudder. The power of odors to activate memories both pleasing and aversive exists in many animals, from humans to the humble fruit fly.
Scientists on the Florida campus of The Scripps Research Institute (TSRI), writing in the journal *Cell Reports*, detailed how the intricate biochemical mechanism for storing scent-associated memories differs slightly from a less-understood mechanism for erasing unnecessary memories.

Understanding how brains actively erase memories may open new understanding of memory loss and aging, and open the possibility of new treatments for neurodegenerative disease.

In multiple ways, the processes of forgetting and remembering are alike. In fruit fly models of odor-associated learning, both the saving and erasure of memories involves dopamine activation of the brain cells. This clue in flies is important for understanding the human brain.

“The olfactory systems of flies and humans are actually quite similar in terms of neuron types and their connections,” said study leader Ron Davis, Ph.D., co-chair of TSRI’s Neuroscience Department.

Also, in both cases, activation of the neurons causes them to make an identical messenger molecule, cyclic AMP, leading to a cascade of activity within the cell, either building or breaking down memory storage, added Davis.

“So how do the cells know when they are getting a forgetting signal verses an acquisition signal? That was the huge, perplexing question,” Davis said.

TSRI Professor Kirill Martemyanov, Ph.D., and Staff Scientist Ikuo Masuho, Ph.D., found that a type of signaling protein in neurons played a role. Masuho and Martemyanov screened a panel of these signaling proteins, called G proteins, against cells that expressed two key receptors known to be involved in memory and forgetting.

The TSRI team found one G protein, called G alpha S, that latched on to a neural dopamine receptor called dDA1, associated with memory formation. They found a different G protein, called G alpha Q, linked up with a nearby dopamine receptor called Damb, associated with the machinery of forgetting.

The next question was whether those two different G proteins could be controllers of the fly brain's memory machinery. To find out, the researchers silenced genes involved in the production of the G alpha Q protein in the flies. The flies with the protein silenced were exposed to odors in aversive situations and sent through mazes to see how well they remembered to turn away in the presence of the scent.

"If you removed G alpha Q, the flies should not forget, and indeed, they did not," Davis said. "They remembered better."

It appears in flies that some level of forgetting is a constant, healthy process, he said.

"The idea is, constantly as we learn information, there is a slow process that whittles away memories, and it continues whittling them away unless another part of the brain signals the memory is important and overrides it," Davis said.

It may be that the process of acquiring and forgetting memories ebbs and flows in a state of balance, he said. Important memories like the taste of mom's pumpkin pie might be forever retained, but trivialities like what you wore 10 years ago can fade into oblivion without consequence.

"If you have too much memory that is old and unnecessary, why keep them around? Why shouldn't you have a system for removing those for optimal function of the brain?" Davis asked. "We're getting all this information, all this learning during the day, and the brain may be saying, 'No, no, bring me back to my basal, my happy state.'"

Many questions remain to be solved, Davis noted. "We need to figure out what is downstream—walk down the pathway to find the complete signaling system for forgetting," he said. "We are very early in this research."

In addition to Davis, other authors of the study, "Dopamine Receptor DAMB Signals via Gq to Mediate Forgetting in Drosophila," include first authors Sophie Himmelreich and Ikuo Masuho, as well as Jacob A. Berry, Courtney MacMullen, Nickolas K. Skamangas and Kirill A. Martemyanov.

Research in the Davis laboratory was supported by grants 4R37NS019904, 5R01NS052351, and 1R35NS097224 from NINDS. Research in the Martemyanov laboratory was supported by grants DA036596 and DA026405 from NIDA, and MH105482 from NIMH. The authors thank TRiP at Harvard Medical School (NIH/NIGMS R01-GM084947 ) and Janelia Farms for providing transgenic fly stocks used in this study.

**Scientists discover possible master switch for programming cancer immunotherapy**

JUPITER, FL – December 11, 2017 - During infection or tumor growth, a type of specialized white blood cells called CD8+ T cells rapidly multiply within the spleen and lymph nodes and acquire the ability to kill diseased cells. Some of these killer T cells then migrate where required to vanquish the germs or cancers.

But how do killer T cells "learn" to leave their home base and amass within specific tissues like the skin, gut, and lung, or solid tumors? Finding the factors that cause T cells to function beyond the lymphoid system and in sites of infection or cancer has proven a tough challenge, but it's essential for developing cancer-fighting immunotherapy strategies.

Writing in the journal *Nature*, researchers from The Scripps Research Institute and the University of California, San Diego report the discovery that a protein called "Runx3" programs killer T cells to establish residence in tumors and infection sites.

"Runx3 works on chromosomes inside killer T cells to program genes in way that enables the T cells to accumulate in a solid tumor," said Matthew Pipkin, Ph.D., associate professor in the Department of Immunology and Microbiology on the Florida campus of The Scripps Research Institute.

The paper, "Runx3 programs CD8+ T cell residency in non-lymphoid tissues and tumors," appears in *Nature's* Dec. 14 issue.

There are two main strategies in cancer immunotherapy that employ killer T cells, Pipkin said. Checkpoint inhibitor blockade unleashes killer T cells, prompting them to accumulate in tumors more aggressively. Adoptive cell transfer, meanwhile, involves re-infusing a patient's own immune cells after they have been engineered in the lab to recognize and destroy the patient's specific cancer.

The adoptive cell transfer strategy has worked stunningly well in some blood cancers associated with the lymphoid system, so far. But there appears to be less efficient activity of T cells in solid tumors, Pipkin said.

"The gene programs and signals for how the T cells take up residence in tissues outside of the general circulation was not really well understood," Pipkin said.

To discover factors that control T cell residency beyond the lymphoid system, Pipkin's team worked collaboratively with the laboratory of UC San Diego's Ananda Goldrath, who compared the gene expression of CD8+ T cells found in non-lymphoid tissue to those found in the general circulation. From a list of potential factors, they employed an RNA interference screening strategy which can test the actual function of thousands of factors simultaneously. Pipkin's lab had developed the screening strategy in collaboration with Shane Crotty at the La Jolla Institute for Allergy and Immunology.

"We found a distinct pattern," Pipkin said. "The screens showed that Runx3 is one at the top of a list of regulators essential for T cells to reside in nonlymphoid tissues." Moreover, Runx3 was able to engage a specific gene program that is found in natural tissue-resident and tumor infiltrating CD8+ T cells, he said.

The group further assessed whether Runx3 had a role in directing white blood cells that attack solid tumors in mouse melanoma models. They found that adoptive cell transfer of cancer-specific killer T cells that overexpressed Runx3 delayed tumor growth and prolonged survival, while mouse models treated with those lacking Runx3 fared much worse than normal.

"If we enhance Runx3 activity in the cells, the tumors are significantly smaller and there is greater survival compared to the control group," Pipkin said.

Knowing that modulating Runx3 activity in T cells influences their ability to reside in solid tumors opens new opportunities for improving cancer immunotherapy, Pipkin said.

"The upshot is we could probably use Runx3 to reprogram adoptively transferred cells to help drive them to amass in solid tumors," he said. He added that a collaboration of specialists energized the research. "It was a fantastic collaboration, it all came together very quickly," Pipkin said.

*In addition to Pipkin, Adam Getzler and Dapeng Wang of TSRI, lead author Justin Milner, and Goldrath of UCSD, the co-authors of "Runx3 programs CD8+ T cell residency in non-lymphoid tissues and tumors," include Clara Toma, Bingfei Yu, Kai Zhang, Kyla Omilusik, Anthony Phan, Toan Nguyen, Wei Wang and Shane Crotty.*

*The research was supported by Frenchman's Creek Women for Cancer Research (D.W.) and UCSD Molecular Biology Cancer Fellowship (J.J.M.), the National Institutes of Health U19AI109976 (S.C., M.E.P., A.W.G) and R01AI095634 (M.E.P.), California Institute for Regenerative Medicine RB5-07012 (W.W.), the Kimmelman Family Foundation and the San Diego Center for Precision Immunotherapy (A.W.G.).*

**Blueprints for anti-cancer drugs discovered in bacterial genomes**

JUPITER, FL – December 11, 2017 - Scientists on the Florida campus of The Scripps Research Institute (TSRI) who had previously discovered the prostate cancer-killing compound LNM E1 have now brought the family of LNM molecules even closer to clinical testing by "mining" the information stored in bacteria genomes.

Their research suggests these hidden genes hold the blueprints for designing new, even more effective cancer-targeting compounds. "This points the way toward a new therapeutic opportunity," says lead investigator Ben Shen, Ph.D., TSRI professor and co-chair of the Department of Chemistry. The findings were published today in the journal *Proceedings of the National Academy of Sciences USA.*

**Unlocking anti-tumor molecules in nature**

The leinamycin (LNM) family is a group of compounds called natural products, produced by a bacterium that lives in soil. Until now, Shen and his colleagues were only aware of one member of the LNM family, a compound called LNM. By editing the genome of the bacterium, the Shen lab produced LNM E1, which they showed in 2015 could react with reactive oxygen species in prostate cancer cells, triggering death.

"So we knew the molecule was useful, but then what? We needed to make many variants to optimize efficacy in animal models," says Shen.

Unfortunately, synthesizing LNM E1 to make analogues has proven challenging because of the compound's complicated structure.

The lack of analogues led Shen and his colleagues to look to nature for help. Luckily, researchers have a valuable resource on TSRI's Florida campus, where Shen heads the Natural Products Library

Initiative, a library consisting of purified natural products, partially pure fractions, crude extracts and bacterial strains collected from all over the globe that are available for screening.

By combing through this library and public datasets, the team discovered 49 bacteria with genes that appear to code for members of the LNM family. The researchers confirmed this finding through bioinformatics analysis and by isolating several of the newly discovered LNM compounds in the lab.

With this research, Shen and his colleagues now have an idea of the structural diversity in LNMs. They found that while bacteria evolved to have LNMs with many of the same characteristics, small changes, such as atomic differences in the building blocks of their core scaffolds, could make some LNMs more or less effective against cancer cells. The next step will be to study LMN molecule interactions with cancer cells to find out.

This finding represents a big shift in how scientists discover natural product drug candidates. Shen explained that for a long time, scientists had to cast a wide net to discover potential medicinal compounds, more or less by chance, in animals, plants, bacteria and fungi. With the more focused, genome-driven technique employed at TSRI, scientists can close in on suspected sources of a potential drug more efficiently, in this case, mining bacteria genomes to find the instructions for making LNMs.

“The technological advances we’ve made enable us to quickly identify sources of these types of natural products,” says Shen. “This could dramatically impact the drug lead pipeline.”

*TSRI Research Associates Guohui Pan and Zhengren Xu served as co-first authors of the study “Discovery of the Leinamycin Family of Natural Products by Mining Actinobacterial Genomes,” which also included authors from Ghent University, Belgium; Central South University and Yunnan University, China; and Myongji University, Korea.*

*The study was supported by the Chinese Ministry of Education 111 Project B08034, National High Technology Joint Research Program of China (grant 2011ZX09401-001), and National High Technology Research and Development Program of China (grant 2012AA02A705); the Cooperative Research Program for Agriculture Science & Technology Development, Rural Development Administration, Korea (Project No. PJ01128901); and the National Institutes of Health (grant CA106150).*

**Dysfunctional gene may be culprit in some Crohn’s disease cases**

JUPITER, FL – January 12, 2018 - A study from the lab of biologist Mark Sundrud, Ph.D., on the Florida campus of The Scripps Research Institute (TSRI), has shown that genetics plays a role for some people with Crohn’s disease, a potentially powerful discovery for people with a specific mutation. An inexpensive and effective treatment may already be readily available for them, Sundrud said.

Additional trials in the clinic are planned to help refine who can benefit, and develop a diagnostic test that could enable some Crohn’s patients to forego costlier, less effective treatments like steroids, Sundrud said.

“Our data suggests this could be life-changing for a group of Crohn’s patients,” Sundrud said. “People with severe, chronic Crohn’s who are not helped by current medications could benefit.”

Crohn's disease involves inflammation of the digestive tract. It can become so severe that patients can develop malnutrition, weight loss and fatigue from the severe diarrhea and pain. Difficult and even life-threatening complications such as bowel obstructions, colon cancer, blood infections, or sepsis can develop. A common treatment, corticosteroids by pill or IV, can cause serious side-effects such as weight gain, osteoporosis, unstable blood sugar and other problems. Approximately 360,000 people in the United States suffer from Crohn's disease, causing nearly 190,000 hospitalizations annually, according to the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health.

A subset of those patients has a type that involves an inability to reabsorb excess digestive fluids in the ileum, or the last section of the small intestine, Sundrud said. The imbalance can lead to intestinal injury and pain—sometimes severe. The culprit is a digestive acid called bile. Made in the liver, it seeps into the gut during consumption of a big meal. Bile helps with the digestion of fats, releasing important nutrients into the body.

Bile is chemically similar to detergent, however, so too much can lead to inflammation and potentially injure the intestinal lining. Some probiotics have been shown to help a bit with maintaining the appropriate amount of digestive fluids, but it wasn't known if genetic factors played a role, too, Sundrud said.

Sundrud's team discovered that a type of circulating immune system cell called a T helper cell 17, or TH17, can play an important role in digestion. When those circulating cells reach the end part of the small intestine, if they encounter too much bile, they adapt by switching on production of a gene called MDR1, Sundrud said. That was a surprise. Previously, MDR1 was known to transport chemotherapeutic drugs out of tumor cells, he said, but its role in aiding digestion wasn't understood. Sundrud and his team found that if the MDR1 gene is not present in those circulating immune cells, or is mutated in a way that makes it ineffective, bile acids can accumulate in the ilium and injure the intestine. The research was published Dec. 19, 2017, in the journal *Immunity*.

"About 10 percent of patients with Crohn's disease have disease that is driven by bile reabsorption issues," Sundrud said.

Sundrud is hoping to attract funding for a clinical study to take the work further. Sundrud and his graduate student, Mei Lan Chen, are continuing to study how TH17 cells adapt within the body. And working with a team of clinicians at the University of Miami, he hopes to recruit Crohn's patients to discern the healthy vs. disease-promoting range for MDR1 mutations, potentially giving doctors more options to help Crohn's patients.

"You can efficiently prevent this with a type of medication called a bile acid sequestrant. It's a packet of powder that goes on food," Sundrud said. "This could be much a less expensive therapy for those patients than other alternatives."

*In addition to Sundrud, co-authors of the study were Wei Cao, Mei Lan Chen, Amber Delmas, Erumbi S. Rangarajan, Kelly McKevitt, Cody B. Jackson, Tina Izard and Gogce Crynen, all of The Scripps Research Institute; Hisako Kayama and Kyoshi Takeda of Osaka University; Amy Sun, Sergei B. Koralov and Sang Yong Kim of New York University Medical Center; Amanda P. Beck of MD Anderson Cancer Center; Angelos Oikonomopoulos, Precious N. Lacey and Daniel W. Hommes of University of California, Los Angeles; Gustavo Martinez of Rosalind Franklin University of*

*Medicine and Science; Robin G. Lorenz of University of Alabama; Alex Rodriguez-Palacios and Fabio Cominelli of Case Western Reserve University; and Mari T. Abreu of the University of Miami.*

*This work was funded by TSRI Florida via the State of Florida, the National Institute of Allergy and Infectious Diseases (grant R21AI119728.), the National Institute of Diabetes and Digestive and Kidney Diseases (5R01DK099076-07 andP01DK071176), the Crohn's and Colitis Foundation of America (#422515, #3786 and #26971), the Broad Medical Foundation (#IBD-0389R), and the Core Research for Evolutional Science and Technology, Japan Science and Technology Agency; the Ministry of Education, Culture, Sports, Science and Technology; and the Ministry of Health, Labour and Welfare, a Lotte Research Promotion Grant and the Nagao Memorial Fund.*

*Mari T. Abreu and Daniel W. Hommes have received research grants and consultancy fees from: AbbVie, Amgen, Asana Medical, Inc., Ferring Pharmaceuticals, Focus Medical Communications, Genentech, Genova Diagnostics, GI Health Foundation, Gilead, GSK Holding Americas, Inc., Hospira, Inc., Janssen, Mucosal Health Board, Pfizer, Prometheus Laboratories, Prova Education, Inc., Sanofi Aventis, Shire, Takeda, UCB and WebMD Health.*

**TSRI researchers identify gene responsible for mesenchymal stem cells' stem-ness'**

JUPITER, FL – January 22, 2018 - Many doctors, researchers and patients are eager to take advantage of the promise of stem cell therapies to heal damaged tissues and replace dysfunctional cells. Hundreds of ongoing clinical trials are currently delivering these therapies to patients worldwide.

Mesenchymal stem cells (MSCs) are popular tools for these therapies because they can differentiate into a variety of mature cell types such as bone, fat and cartilage. They also support hematopoiesis—the formation of blood cells—and secrete beneficial factors that promote tissue repair. Unfortunately, scientists often struggle to predict how these cells will act in different environments in the body.

Researchers on the Florida campus of The Scripps Research Institute (TSRI) recently published a study in the journal *Cell Death and Differentiation* identifying factors crucial to MSC differentiation, providing insight into how these cells should be studied for clinical purposes.

Primary MSCs from bone marrow are delicate, and it´s difficult to keep them alive in a petri dish. For this reason, most scientists studying them use cell lines, cells that have been altered to live and replicate indefinitely. To create immortal MSC lines, scientists delete a gene called p53 required for the cells to undergo normal, programmed cell death, called apoptosis. The new study, conducted by researchers in the lab of TSRI Professor Donald Phinney, PhD, shows that the gene influences far more than just apoptosis; it is also a master regulator of the cells' ability to differentiate.

"Many publications have used immortalized cells as MSC surrogates, but they may not mean much if they don't have functionally accurate p53," says Siddaraju Boregowda, PhD, a TSRI research associate and one of the study's two lead authors.

The researchers compared cells cultured from mice that did not express the p53 gene with cells that came from normal mice. They found that the level of active p53 was the master regulatory factor in determining how MSCs grow and differentiate. The study explains that the gene exerts its effects through its interactions with reactive oxygen species as well as two transcription factors: TWIST2 and PPARG.

When the researchers deleted p53 completely, the cells became immortal but quickly developed into bone. They lost their ability to promote hematopoiesis or become other types of cells, like fat. A low level of p53 induced TWIST2, which kept the MSCs in a stem state, rather than promoting any differentiation. A slightly higher level of p53 induced PPARG and reactive oxygen species, which led the cells to differentiate into fat cells, but not bone. At even higher levels of p53, the cells died.

A basal level of p53 in cells in the culture is required for them to act as an accurate model for cells in the body, explains Veena Krishnappa, PhD, the study's other lead author, previously a postdoctoral researcher in Phinney's lab.

In addition to suggesting that the dramatic effects of deleting p53 may make MSC cell lines an inappropriate surrogate to predict the cells' behavior in clinical applications, the study also suggests that inactivation of p53 may play multiple roles in the progression of bone cancers.

"P53 inactivation not only promotes sustained growth but also makes the cells insensitive to oxidative stress and short-circuits pathways that constrain cellular differentiation. Each of these changes likely contribute significantly to tumorigenesis and tumor progression," says Phinney. "Continuing to delineate the important role of MSCs in skeletal disease may open the door to devising new therapeutic interventions."

*In addition to Boregowda, Krishnappa and Phinney, authors of the study, "Basal p53 expression is indispensable for mesenchymal stem cell integrity," include Jacqueline Strivelli, Christopher L. Haga and Cori N. Booker of The Scripps Research Institute.*

*This work was supported by funding from the National Institutes of Health (grant R24 OD18254).*

*Cover photo courtesy National Institutes of Health, Chun Yang, Hao Ma and Anouk Killaars, University of Colorado Boulder*

**New TSRI research points to better way to treat depression**

JUPITER, FL – March 01, 2018 - Scientists on the Florida campus of The Scripps Research Institute (TSRI) have discovered a new target for treating major depressive disorder, a disease that affects more than 16 million American adults. Their research shows that individuals with high levels of an enigmatic receptor called GPR158 may be more susceptible to depression following chronic stress.

"The next step in this process is to come up with a drug that can target this receptor," says Kirill Martemyanov, PhD, co-chair of the TSRI Department of Neuroscience and senior author of the new study, published recently in the journal *eLife*.

The researchers say there is an urgent need for new drug targets in major depressive disorder. Current pharmacological treatments for depression can take a month to start working—and they don't work in all patients.

"We need to know what is happening in the brain so that we can develop more efficient therapies," says Cesare Orlandi, PhD, senior research associate at TSRI and co-first author of the study.

The researchers zeroed in on GPR158 as a player in depression after discovering that the protein is elevated in people with major depressive disorder. To better understand GPR158's role, the scientists studied male and female mice with and without GPR158 receptors.

Behavioral tests revealed that both male and female mice with elevated GPR158 show signs of depression following chronic stress. On the flip side, suppression of GPR158 protects mice from developing depressive-like behaviors and make them resilient to stress.

Next, the researchers examined why GPR158 has these effects on depression. The team demonstrated that GPR158 affects key signaling pathways involved in mood regulation in the region of the brain called prefrontal cortex, though the researchers emphasized that the exact mechanisms remain to be established.

Martemyanov explains that GPR158 is a so-called "orphan receptor" (which gets its name because its binding partner/partners are unknown) with a poorly understood biology and mechanism of action. GPR158 appears to work downstream from other important brain systems, such as the GABA, a major player in the brain's inhibitory control and adrenergic system involved in stress effects.

"This is really new biology and we still need to learn a lot," says Martemyanov.

The study also offers a potential clue to why some people are more susceptible to mental illness. Because mice without GPR158 don't alter their behavior after chronic stress, the researchers concluded these mice were naturally more resilient against depression. Their genetics, or gene expression, offer a layer of protection.

Laurie Sutton, PhD, a research associate at TSRI and co-first author of the study, says this finding matches what doctors have noticed in people who have experienced chronic stress. "There's always a small population that is resilient—they don't show the depressive phenotype," says Sutton.

As the search goes on for additional targets for depression, Martemyanov says scientists areincreasingly using new tools in genome analysis to identify orphan receptors like GPR158. "Those are the untapped biology of our genomes, with significant potential for development of innovative therapeutics," he says.

*Additional authors of the study, "Orphan receptor GPR158 controls stress-induced depression," were Chenghui Song, Brian S. Muntean, Keqiang Xie, Xiangyang Xie and Baoji Xu of The Scripps Research Institute; Won Chan Oh and Rachel Satterfield of the Max Planck Florida Institute for Neuroscience; Alice Filippini of the University of Brescia; Jazmine D. W. Yaeger and Kenneth J. Renner of the University of South Dakota; Samuel M. Young of the Max Planck Florida Institute for Neuroscience and the University of Iowa; and Hyungbae Kwon of the Max Planck Florida Institute for Neuroscience and the Max Planck Institute of Neurobiology.*

*The research was supported by the National Institutes of Health (grants MH105482, HL105550, DA01992, MH107460, 762 DC014093), the University of Iowa, the Max Planck Society and by the Canadian Institutes of Health Research Fellowship.*

**Next-generation arthritis treatments could benefit both horses and humans**

JUPITER, FL – March 02, 2018 - At the Palm Beach International Equestrian Center, members of the riding and jumping community recently heard about studies underway at The Scripps Research Institute (TSRI) and Colorado State University intended to improve their health and that of their elite horses.

TSRI Professor Paul Robbins, PhD, who develops therapies to address cellular senescence and aging-related diseases, has collaborated with David Frisbie, DVM, PhD, and Wayne McIlwraith, DVM, PhD, at Colorado State University's Orthopedic Research Center to advance innovative osteoarthritis treatments for horses and humans.

More than 27 million people live with osteoarthritis, and it turns out, elite racing and jumping horses do, too. Repeated athletic performance can damage cartilage, said Timothy Ober, DVM, senior veterinarian with John R. Steele & Associates and U.S. Team Veterinarian, Show Jumping. Cartilage lacks a blood and nerve supply, and so it generally doesn't heal well on its own. Robbins told the group of about 40 equestrians and veterinarians who attended the Feb. 6 symposium about KA34, a compound discovered at the TSRI-affiliated non-profit the California Institute for Biomedical Research (Calibr). The experimental drug encourages adult stem cells in the joint to mature toward chondrocytes, the cells that produce and maintain healthy cartilage, Robbins said. Robbins said clearing senescent cells, which may drive inflammation and many other diseases of aging, including arthritis, may one day be a complementary therapy to such regenerative approaches.

"We have identified two drugs that actually reduce the level of senescent cells. In animals, speed, endurance and strength improves after treatment," Robbins told the equestrians.

Intervening to prevent early cartilage loss in horses is an important goal, Ober added. "Joint pain and joint inflammation are the biggest challenge we face," Ober said.

**TSRI researchers uncover culprit in Parkinson's brain cell die-off**

JUPITER, FL – March 5, 2018 - An estimated 10 million people worldwide are living with Parkinson's disease—an incurable neurodegenerative disorder that leads to an increasing loss of motor control.
If we could peer into the brains of these patients, we'd see two hallmarks of the disease. First, we'd see a die-off of the brain cells that produce a chemical called dopamine. We'd also see protein clumps called Lewy bodies inside the neurons.

Corinne Lasmézas, DVM, PhD, a professor on the Florida campus of The Scripps Research Institute (TSRI), believes a key to treating Parkinson's is to study possible links between these two phenomena.

Now her group has discovered a connection between neuronal death and Lewy bodies. The research, published recently in the journal *Proceedings of the National Academy of Sciences*, offers an explanation for why neurons die off in the first place.

'This study identifies the missing link between Lewy bodies and the type of damage that's been observed in neurons affected by Parkinson's," says Lasmézas, senior author of the study.
"Parkinson's is a disorder of the mitochondria, and we discovered how Lewy bodies are releasing a partial break-down product that has a high tropism for the mitochondria and destroys their ability to produce energy."

**Toxic protein travels to mitochondria to do damage**

Lewy bodies were described a century ago, but it was not until 1997 that scientists discovered they were made of clumps of a misfolded protein called α-synuclein. When it's not misfolded, α-synuclein is believed to carry out functions related to the transmission of signals between neurons.

Lasmézas' research focuses on neurological disorders caused by misfolded proteins, such as Alzheimer's, Parkinson's, prion diseases, frontotemporal dementia and amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). She uses lab models, including cell cultures and mice, to study these diseases.

In the current study, Lasmézas and her team looked at cell cultures of neurons that were induced to accumulate fibrils made of misfolded α-synuclein, mimicking Lewy bodies in patients with Parkinson's. They discovered that when α-synuclein fibrils are broken down, it often creates a smaller protein clump, which they named pα-syn* (pronounced "P-alpha-syn-star").

"Sometimes the nerve cells can efficiently degrade the α-synuclein fibrils, but if they get overwhelmed, the degradation may be incomplete," she explains. "And it turns out that the result of that partial degradation, pα-syn*, is toxic."

Diego Grassi, PhD, a research associate in Lasmézas' lab, made this discovery by labeling the pα-syn* with an antibody so he could follow it throughout the cell after it was created. He observed that pα-syn* traveled and attached itself to the mitochondria. Further investigation revealed that once the pα-syn* attached, the mitochondria started to break down. These fragmented mitochondria lose their ability to carry an electrochemical signal and produce energy.

The researchers followed up with an analysis of mouse and human brain samples. They confirmed the existence of pα-syn* in the dopamine-producing neurons.

"The Lewy bodies are big aggregates and they're sitting in the cell, but they don't come into direct contact with the mitochondria in the way pα-syn* does," Lasmézas explains. "With Diego's discovery, we've made a direct connection between the protein α-synuclein and the downstream effects that are observed when brain cells become damaged in Parkinson's."

Lasmézas plans to continue studying the connection between misfolded proteins and the destruction of mitochondria in neurons. "What we found may not be the only mechanism of toxicity, but we know it's important," she says. "This paper is about identifying where pα-syn* comes from and what it does to the mitochondria, but there's obviously, mechanistically, a lot that we still don't know."

She says that these findings also have implications for designing treatments for Parkinson's, noting that some drugs currently under development are focused on getting rid of larger fibrils that make up Lewy bodies.

"It's important to be aware that when Lewy bodies are broken down, these toxic substances may be created," Lasmézas says. In addition, she adds, the discovery of pα-syn* as an important component of the disease process points to a new target for creating drugs slowing disease progression.

*First author of the study, "Identification of a highly neurotoxic α-synuclein species inducing mitochondrial damage and mitophagy in Parkinson's disease," was Diego Grassi. Other authors*

*were Shannon Howard, Minghai Zhou, Natalia Diaz-Perez, and Philip LoGrasso of The Scripps Research Institute; Nicolai T. Urban, Debbie Guerrero-Given, and Naomi Kamasawa of the Max Planck Florida Institute for Neuroscience; and Laura Volpicelli-Daley of the University of Alabama at Birmingham.*

*This research was funded by the National Institute of Neurological Disorders and Stroke (grant R01NS085223), the Michael J. Fox Foundation and the Saul and Theresa Esman Foundation.*

**Your immune system holds the line against repeat invaders, thanks to this molecule**

JUPITER, FL – April 17, 2018 - Memory T cells are a critical element of our immune system's historical archive. To prevent repeat infections, these cells retain a record of germs they've fought before.
But for all their importance, the origins of memory T cells have remained a mystery.

Now, a new study from the laboratory of immunologist Matthew Pipkin, PhD, of The Scripps Research Institute's Florida campus, lays out the opening chapter of this enigma.

Researchers found a transcription factor protein called Runx3 puts dividing T cells on track to becoming memory T cells. This new insight may allow researchers to design drugs that improve immune responses to vaccines, Pipkin says. The discovery could also have implications for chronic diseases such as cancer, in which responding T cells sometimes become "exhausted" and unable to rally an effective defense.

"There are instances such as chronic infection and tumors where the T cells differentiate in an aberrant way that shortens their life span and decreases their function," Pipkin says. "Because our study found that Runx3 is one of the earliest players during an immune response, manipulating it might be an avenue to basically turn back the clock and reprogram dysfunctional T cells into a format that is conducive to them developing into genuine memory cells that are protective."

The study, "The transcription factor Runx3 establishes chromatin accessibility of *cis*-regulatory landscapes that drive memory cytotoxic T lymphocyte formation," appears online in the journal *Immunity* on April 17, 2018.

**Runx3 coordinates a rapid memory cell response**

Runx3's control of T cell differentiation is important because when our bodies fight off viruses and cancers—and our T cells burst into action—the vast majority tend to become effector cells. These effector cells are short-lived and do not persist once the infection resolves.

The amount of Runx3 has a deterministic effect on the outcome of the differentiation of the T cells, Pipkin says. Runx3 controls that burst of activity and ensures the cells are directed toward a different fate, that of memory T cells, which can live for decades.

"This finding provides molecular evidence that the programming of memory is established very rapidly, and that it's kind of a push and pull to restrain the developing memory cells from differentiating into effector cells, which is a dead-end road," says Pipkin.

The team studied what happened when Runx3 expression was partially suppressed using RNA interference. “All those experiments showed you lost the known precursors that give rise to memory T cells,” Pipkin says. Conversely, cells with experimentally increased Runx3 produced more memory T cells.

Cells with increased Runx3 were also better at regenerating new rounds of memory cells than normal cells after repeated infections with *lymphocytic choriomeningitis virus* (LCMV) and *Listeria monocytogenes*. This indicated that Runx3 enhances memory T cell potential, Pipkin says.

“Our work demonstrates that Runx3 turns down another transcription factor that commits the cells to becoming these terminal effector cells, and it slows down proliferation. That keeps the cells on a trajectory into the memory lineage.”

The new study also sheds light on the timeline when immune memory is established against an invader. Researchers found molecular evidence that the programming of memory T cells happens very rapidly after the immune system first encounters new threats. At this time, naïve CD8+ T cells must begin developing into specialists called cytotoxic T lymphocytes (CTL), that can kill infected or malignant cells. Pipkin’s lab found that Runx3 coordinates the memory T cell differentiation program within the first few hours of infection.

Pipkin and his colleagues discovered the critical role of Runx3 in T cell differentiation by challenging naïve T cells with an antibody signal that mimicked infection, and then mapping the areas of the newly exposed genome. This revealed that the locations on our chromosomes where Runx3 binds became receptive to binding immediately after infection, and before the first CD8+ T cell division. These regions were also receptive in fully developed memory T cells, but less so in the terminal effector cells.

The findings raise many questions, Pipkin adds. He wants to determine if some type of therapeutic could rescue naturally occurring Runx3 deficiencies. He also wants to identify the other players that cooperate with Runx3.

“We know that Runx3 is working with a number of additional transcription factors and chromatin regulatory proteins,” Pipkin says. “So, we are currently trying to identify them and determine how they collaborate with Runx3 to turn on and off different regions of the genome to promote memory development.”

*In addition to Pipkin, the authors of the study include first author Dapeng Wang, Huitian Diao, Adam J. Getzler, Walter Rogal and Megan Frederick of The Scripps Research Institute; Justin Milner, Bingfei Yu and Ananda Goldrath of the Division of Biological Sciences at the University of California, San Diego; and Shane Crotty of the La Jolla Institute for Allergy and Immunology and the UC San Diego School of Medicine.*

*The research was supported by Frenchman’s Creek Women for Cancer Research and the National Institutes of Health (grants R01 AI095634 (M.E.P.) and NIH U19 AI109976).*

**Tumor-like spheres help scientists discover smarter cancer drugs**

JUPITER, FL – May 14, 2018 - Cancer is a disease often driven by mutations in genes. As researchers learn more about these genes, and the proteins they code for, they are seeking smarter

drugs to target them. The ultimate goal is to find ways to stop cancer cells from multiplying out of control, thereby blocking the growth and spread of tumors.

Now researchers from The Scripps Research Institute are reporting an innovative new method to screen for potential cancer drugs. The technique makes use of tiny, three-dimensional ball-like aggregates of cells called spheroids. These structures can be used to interrogate hundreds or even thousands of compounds rapidly using a technique called high throughput screening. In fact, by using this approach, the team has already identified one potential drug for an important cancer gene. The results were reported in the journal *Oncogene*.

"We can now do studies using a form of cancer cells that is more physiologically relevant and better recapitulates how these cells appear in the body," says Timothy Spicer, director of Lead Identification Discovery Biology and High Throughput Screening on Scripps Research's Florida campus and one of the study's corresponding authors.

"Until now, most of the research to screen for cancer drugs has used cells that are growing flat on a plate," adds Louis Scampavia, director of HTS Chemistry and Technologies at Scripps Research and one of the study's co-authors. "With these 3-D spheroids, we emulate much more closely what's found in living tissues."

The spheroids are 100 to 600 microns in diameter—equivalent to the thickness of a few sheets of paper. In contrast to single layers of cells normally used to screen for drugs, which tend to all grow at the same rate because they get the same exposure to oxygen and nutrients, the spheroids mimic what might happen in a tumor: Some cells are on the outside and some are on the inside.

In the new paper, the researchers focused on a cancer-driving protein called *KRAS*. The *KRAS* gene and other members of the related *RAS* gene family are found to be mutated in nearly one-third of all cancers. They are common in lung cancer, colorectal cancer, and especially pancreatic cancer. In fact, up to 90 percent of pancreatic cancers are driven by *KRAS* mutations, and the investigators used pancreatic cancer cell lines for the current study.

"In the past, *KRAS* has been a very tricky protein to target. People have spent several decades trying, but so far there has been little success," says Joseph Kissil, PhD, professor at Scripps Research Medicine and the other co-corresponding author. "The KRAS protein is relatively small, and that's made it hard to attack it directly. But the method of screening that we used in this study allowed us to come at the question in a different way."

The investigators performed what is called a phenotypic screen, which means they were looking for drugs that had an effect on cell growth, but didn't have a preconceived idea about how they might work. "We came at this in an unbiased way," Kissil explains. "We were not trying to design something to attack a specific part of the KRAS protein. We were just looking for something that acted on some part of the pathway that's driving cell growth."

The investigators report in the new paper that they have already identified one compound that was previously not know to affect *KRAS*, called Proscillaridin A. The compound is similar to a class of drugs used to treat some heart conditions. Although the team says this particular drug is unlikely to be developed as a cancer treatment, it validates the approach of conducting drug screenings using

spheroids. “It’s unlikely we would have discovered this connection using standard 2-D methods,” Scampavia says.

“From our perspective, this is a proof-of-principle study,” Kissel adds. “It shows you can look at libraries of drugs that have already been approved for other diseases, and find drugs that may also work for cancer. In theory, you could use this screening method for any line of cancer cells, and any mutation you want.”

“We would love to use this research to create a pipeline for new oncology drugs,” Spicer concludes. “Many of the most promising compounds may be overlooked with 2-D screening. This study provides direct evidence that screening for drugs using 3-D structures of cancer cells may be more appropriate.”

*Other authors of the study,* “A Novel 3-dimensional High Throughput Screening Approach Identifies Inducers of a Mutant KRAS Selective Lethal Phenotype*,” were Smitha Kota, Shurong Hou, William Guerrant, Franck Madoux, Scott Troutman, Virneliz Fernandez-Vega, Nina Alekseeva and Neeharika Madala of Scripps Research.*

*This work was supported in part by the National Cancer Institute of the National Institutes of Health (grants R33CA206949 and CA124495).*

**Autism research to advance with $3.6 million NIH grant to Scripps Florida team**

JUPITER, FL – May 22, 2018 - Gavin Rumbaugh, PhD, of The Scripps Research Institute’s Florida campus, will lead a 5-year, $3.6 million grant from the National Institute of Mental Health to continue studies of abnormal brain circuitry in autism.

The grant builds upon previous work from the Rumbaugh lab that uncovered a sensitive period in brain development during which an autism and intellectual disability risk gene called *Syngap1* must function properly to promote assembly of circuitry needed for healthy social and cognitive development.

With the new funding, the team plans to focus on how this *Syngap1*sensitive period regulates developmental processes that link sensory processing to learning, and how harmful *Syngap1* mutations may lead to autism-associated behavioral changes through sensory dysfunction.

Sensory processing impairments are nearly universal in children with neurodevelopmental disorders, such as autism and intellectual disability. However, it is unclear how and where in the brain altered sensory processing impairs learning and drives altered behaviors in these disorders.

“Our *Syngap1* animal models are an excellent way to investigate the direct neurobiological links between autism-associated sensory processing impairments and behavioral changes also seen in these children,” Rumbaugh says. “Understanding how these processes are linked is critical to identifying the brain circuits that are not functioning properly and contributing to the cause of these disorders.”

The work will be performed in collaboration with Scripps Research Associate Professor Courtney Miller, PhD, and Jason Christie, PhD, a researcher at the Max Planck Florida Institute for

Neuroscience. The proposed studies require the real-time measurement of brain activity in *Syngap1* mice undergoing behavioral training in a variety of sensory detection tasks. Miller's expertise in developing complex rodent behavioral paradigms, and Christie's successful adoption of emerging tools to measure brain activity in behaving animals, are critical to the project, Rumbaugh says.

"This project reflects the growing need for researchers with diverse expertise to collaborate in order to solve important problems in neuroscience," Rumbaugh says.

The number of the grant is R01 MH096847.

**The Scripps Research Institute sets the stage for 26th commencement ceremony**

LA JOLLA, CA and JUPITER, FL – May 15, 2018 – The Skaggs Graduate School of Chemical and Biological Sciences at The Scripps Research Institute will hold its 26th commencement ceremony on May 18, awarding graduate degrees to 42 students. This will be one of the biggest ceremonies with 13 graduates from the Florida campus.

"The graduates of the Class of 2018 are a group of dedicated and creative researchers," says Phil Dawson, Ph.D. dean of the graduate program and an alumnus from the Class of 1996. "It's amazing to see what they've accomplished in so many fields—from new insights into infectious disease and cellular biology to new reactions and drug development tools."

For the last 19 years, the Skaggs Graduate School of Chemical and Biological Sciences has been ranked among the top ten in the nation according to a recent survey by U.S. News & World Report. Since its founding in 1989, over 100 alumni have gone on to hold faculty positions at major universities and colleges around the world. Hundreds more alumni have earned leadership roles in biotech and pharmaceutical companies.

At this year's ceremony, the graduate program will also confer honorary doctorates on genetic engineering pioneer Herbert Boyer, PhD, and groundbreaking chemist JoAnne Stubbe, PhD.

Boyer is a Scripps Research board member, and he is internationally recognized for his pioneering discovery of recombinant DNA, which has led to numerous life-saving medicines. He co-founded Genentech in 1976 with the late venture capitalist Robert Swanson, breaking new ground for both life science technology and new business models. Boyer is now retired and is Professor Emeritus of Biochemistry and Biophysics at the University of California, San Francisco.

Stubbe is a chemist who has spent her career studying the enzymes that make life possible-work that earned her the National Medal of Science in 2009. Among many notable discoveries, her studies led to the development of the pancreatic cancer drug gemcitabine. Stubbe currently serves as is the Novartis Professor of Chemistry & Biology Emerita at the Massachusetts Institute of Technology.

**Novel RNA-modifying tool corrects genetic diseases, including driver of triple-negative breast cancer**

JUPITER, FL – May 29, 2018 - As scientists gain insights into which genes drive diseases, they are pursuing the next logical question: Can gene editing technologies be developed to treat or even cure those diseases? Much of that effort has focused on developing technologies such as CRISPR-Cas9, a protein-based system.

At The Scripps Research Institute campus in Florida, chemist Matthew D. Disney, PhD, has taken a different approach, developing a small-molecule-based tool that acts on RNA to selectively delete certain gene products.

Disney's deletion tool opens the possibility of creating drugs that can be taken conveniently as pills to correct genetic diseases—by destroying toxic gene products, and by chemically controlling the body's defense mechanisms. The paper, "Small molecule targeted recruitment of a nuclease to RNA," was published online by the *Journal of the American Chemical Society*.

"These studies, like much science, were about a decade in the making. We are very excited to see how this initial application evolves," Disney says. "This research further shows that RNA is indeed a viable target to make medicines."

RNAs represent a diverse group of molecules within cells that act like the cells' laborers, reading, regulating and expressing DNA's genetic instructions. Within our cells, RNAs are constantly in motion. They assemble, they carry out their duties, and then they are broken up for recycling by RNA-degrading enzymes, which are chemical scissors that cut apart other molecules.

While about 2 percent of our genome encodes proteins, 70 to 80 percent of the genome is transcribed into RNA, potentially offering significantly more druggable targets, Disney says. Until recently, however, most researchers considered RNAs undruggable, because of their small size and relative lack of stability.

Disney's innovation tethers a drug-like molecule—one engineered to bind precisely and selectively to a specific RNA—to a common RNA-degrading enzyme. The small-molecule/enzyme complex is designed to latch onto the undesirable gene product and destroy it. Disney named the technology RIBOTAC, short for "ribonuclease-targeting chimeras."

To test the RIBOTAC technology, Disney chose for his RNA-degrading enzyme RNase L, which is a critical part of the human antiviral immune response. Present in small amounts in every cell, production of RNase L typically surges on viral infection to destroy the viral RNA and overcome the illness.

For the other piece of the RIBOTAC complex, its drug-like molecule, Disney chose Targaprimir-96, a molecule engineered by his lab in 2016 to bind with a microRNA oncogene known to boost cancer cell proliferation, especially in difficult-to-treat triple-negative breast cancer, miRNA-96.

Destroying the oncogene led to a reawakening of the cancer cell's innate self-destruct program, via an increase in the FOXO1 gene, which ultimately spurred the death of the malignant cells, says Matthew G. Costales, first author of the paper and a graduate student in the Disney lab.

"Anchoring our previous work with Targaprimir-96 to the targeted recruitment of RNase L, we were able to program the RIBOTACs approach to only degrade cells that highly express the miRNA-96 oncogene, thus allowing FOXO1 to signal the selective destruction of triple negative breast cancer cells," says Costales.

Awakening the body's ability to kill its own cancer by exploiting cells' RNA degradation system offers a novel approach to attacking cancer, Disney says. The RIBOTAC technology has potentially broad applications for cancer and other gene-driven diseases as well, he says.

"I believe this is just the tip of the iceberg of how this approach will ultimately be applied," says Disney.

Disney's lab has spent many years developing a computational method called Informa™ to match RNAs with adequate stability and structure to small, drug-like molecules capable of binding to them. His technique led to the development of Targaprimir-96 and multiple other disease-modifying compounds, some of which are now moving toward clinical development.

"Since it is now known that RNA is a key driver in nearly every disease, optimization of this approach that turns a cell's natural defenses toward destroying disease-causing RNAs is likely broadly applicable. We will be laser-focused on diseases for which there are no known cure and have a poor prognosis, such as hard-to-treat cancers and incurable human genetic disease," Disney says. "I am excited to see where we and others ultimately take this."

*In addition to Disney and Costales, co-authors of the study were research associates Yasumasa Matsumoto and Sai Pradeep Velagapudi of The Scripps Research Institute.*

*The work was supported by the Scheller Graduate Student Fellowship and the National Institutes of Health (grant 5RO1GM097455).*

**Two-pronged antibodies draw immune killers directly to cancer cells**

JUPITER, FL – May 30, 2018 - Our immune system's arsenal of defenses usually protects us from cancer. But sometimes, cancer cells overwhelm or evade this elaborate defense system.

In the lab of biochemist and immunologist Christoph Rader, PhD, associate professor at The Scripps Research Institute in Florida, scientists have engineered a new type of anti-cancer antibody, one intended to enhance nature's cancer-fighting strategies by attracting killer T cells directly to cancer cells covered with a distinctive protein.

Dubbed "T-cell engaging bi-specific antibodies," these cancer combatants attack malignant cells but leave healthy cells untouched. That's thanks to their selective targeting system, which zeroes in on a protein found on the surface of several types of cancer cells called ROR1, and also thanks to their talent for binding with T cells, the big guns of the immune system.

"Once the T cells are recruited and activated, they release cytotoxic molecules that penetrate the target cells and kill them," Rader says. "Natural antibodies can't do this. You have to engineer them in a bi-specific fashion to do this."

The scientists' work is described in the article, "Potent and Selective Antitumor Activity of a T-Cell Engaging Bispecific Antibody Targeting a Membrane-Proximal Epitope of ROR1," appearing online May 29 in the journal *Proceedings of the National Academy of Sciences*.

Rader is particularly interested in applying his bi-specific antibodies to a type of breast cancer with fewer treatment options, HER2-negative breast cancer.

"If you look at ROR1 expression in breast cancer, you see that the patients who are HER2 negative are often ROR1 positive," Rader says. "These breast cancer patients might benefit."

Antibodies are proteins made by white blood cells to attack specific targets like viruses, bacteria and cancers. A bi-specific antibody is a Y-shaped immune factor engineered to both bind with a specific disease target, and also to attract killer T cells, a type of white blood cell that destroys infected or dangerous cells.

ROR1 is an excellent target for a smart cancer-fighting system, Rader says, because it is seen only in mature cells that are malignant. Rader first discovered ROR1's activity in leukemia a decade ago while working at the National Cancer Institute.

"ROR1 is expressed during embryogenesis, and then it is tightly down-regulated after birth. It later reappears in both blood cancers and solid malignancies," Rader says.

It has been found on malignant cells including lung, breast, ovarian and blood-based cancers, Rader says.

"One of the most unique aspects of this bi-specific antibody is that it can work in so many different cancer indications," Rader says.

He credits first author Junpeng Qi, PhD, a postdoctoral associate at Scripps Research in Florida, with engineering a group of bi-specific antibodies that stay active in animal models for about five days—a feat compared with current approaches. The U.S. Food and Drug Administration has approved just one bi-specific antibody against cancer so far, against B-cell acute lymphoblastic leukemia. It stays active for a couple of hours, Rader says.

"Junpeng used a component of natural antibodies for this bi-specific antibody that gives it not only a larger size, but also the ability to be recycled and stay in the blood longer," Rader says. "They are not there eternally, though. You get rid of them eventually, which is important for avoiding systemic toxicity."

*Other authors of the study, "Potent and Selective Antitumor Activity of a T-Cell Engaging Bispecific Antibody Targeting a Membrane-Proximal Epitope of ROR1," were Junpeng Qi, Xiuling Li, Haiyong Peng, and HaJeung Park of Scripps Research; and Erika M. Cook, Eman L. Dadashian and Adrian Wiestner of the Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.*

*The research was supported by NIH Grants R01 CA181258 and UL1 TR001114 and by donations from the PGA National Women's Cancer Awareness Days, Peter and Janice Brock, and the Anbinder Family Foundation.*

**Scientists find potential disease-fighting 'warheads' hidden in bacteria**

JUPITER, FL – June 18, 2018 - Bacteria found in soil may harbor a potential game-changer for drug design.

A new study by Scripps Research, published today in *Nature Communications*, suggests scientists could build better drugs by learning from bacteria-derived molecules called thiocarboxylic acids.

The finding comes from Ben Shen, PhD, and his colleagues on the Florida campus of Scripps Research. The team investigates "natural products" made by organisms such as soil-dwelling bacteria.

"We use natural products as an inspiration for chemistry, biology and drug discovery," says Shen, professor and co-chair of the Department of Chemistry at Scripps Research.

Thiocarboxylic acids caught Shen's attention because of their rarity in nature and similarity to lab-made molecules called carboxylic acids. Carboxylic acids are good "warheads" because they can home in on biological targets, making them a key ingredient in many antibiotics, heart disease medications, and more.

Shen and his colleagues took a closer look at two natural products, platensimycin and platencin, that have been extensively investigated as potential antibiotics. Much to their surprise, platensimycin and platencin, which have been known for over a decade to be carboxylic acids, are actually made by bacteria as thiocarboxylic acids.

The researchers revealed, for the first time, the exact genes, and the enzymes they encode, that bacteria use to create thiocarboxylic acids.

From there, the scientists set out to test whether nature-made thiocarboxylic acids could also act as biological warheads. The researchers discovered that, as antibiotics, platensimycin and platencin thiocarboxylic acids appeared to bind to their biological targets even better than their carboxylic acid counterparts.

"That was exciting to see," Shen says. "We've now identified thiocarboxylic acids as natural products that can be used as drugs, and thiocarboxylic acids as warheads should be applicable to man-made drugs as well."

Interestingly, thiocarboxylic acids appear to have been hiding in plain sight. The molecules were thought to be rare and have not been appreciated to date as a family of natural products. Thanks to the current findings, the researchers now know how these producst are made in nature. Upon searching databases of bacterial genomes, the researchers found that many species of bacteria around the world have the genes to produce thiocarboxylic acids.

"There are many, many thiocarboxylic acid natural products waiting to be discovered, making them a treasure trove of potential new drug leads or drugs" says Shen.

*Additional authors of the study, "Biosynthesis of thiocarboxylic acid-containing natural products," were Liao-Bin Dong (first author), Jeffrey D. Rudolf and Nan Wang of Scripps Research; Dingding Kang, Youchao Deng, Yong Huang and Yanwen Duan of the Xiangya International Academy of Translational Medicine, Central South University; and Cyndi Qixin He and K. N. Houk of the University of California, Los Angeles.*

*The research was supported by the Chinese Ministry of Education (111 Project B0803420), the National Institutes of Health (grant GM114353), an Arnold O. Beckman Postdoctoral Fellowship, the Chinese Academy of Sciences and a scholarship from the Chinese Scholarship Council (201504910034).*

**Scripps Research study provides new clues to improving chemotherapies**

JUPITER, FL – June 21, 2018 - About half of all drugs, ranging from morphine to penicillin, come from compounds that are from—or have been derived from—nature. This includes many cancer drugs, which are toxic enough to kill cancer cells.

So how do the organisms that make these toxic substances protect themselves from the harmful effects?

Scientists on the Florida campus of Scripps Research have uncovered a previously unknown mechanism—proteins that cells use to bind to a toxic substance and sequester it from the rest of the organism.

"Thanks to this discovery, we now know something about the mechanisms of resistance that's never been known before for the enediyne antitumor antibiotics," says study senior author Ben Shen, PhD, professor and co-chair of the Scripps Research Department of Chemistry.

The work has important implications for understanding how human cancer cells develop resistance to natural product-based chemotherapies. Furthermore, the microbiome may play a role in drug resistance. The study was published today in the journal *Cell Chemical Biology*.

"This mechanism could be clinically relevant for patients getting these drugs, so it's very important to study it further," says Shen.

Natural products—chemical compounds produced by living organisms—are considered one of the best sources of new drugs and drug leads. "They possess enormous structural and chemical diversity compared with molecules that are made in the lab," Shen says. Natural products may come from flowers, trees or marine organisms such as sponges. One of the most common sources, however, is soil-dwelling bacteria.

Shen's lab is focused on a class of natural products called enediynes. These compounds come from bacteria called actinomycetes, which are naturally found in the soil. Two enediyne products are already FDA approved as cancer drugs and are in wide use. But patients who take them often develop resistance. After a period of months or years, tumors can stop responding to the chemotherapy and begin growing again.

While how patients develop resistance to these drugs remains largely unknown, scientists have uncovered two mechanisms that bacteria use to protect themselves from enediynes. "Mechanisms of self-resistance in antibiotic producers serve as outstanding models to predict and combat future drug resistance in a clinical setting," says Shen.

In the new study, researchers report a third, previously undiscovered resistance mechanism. It involves three genes called *tnmS1*, *tnmS2* and *tnmS3*, which encode proteins that allow bacteria to resist the effects of a type of enediynes called tiancimycins. Shen's lab is currently studying tiancimycins, which hold great promise for new cancer drugs. The proteins work by binding to tiancimycins and keeping them separate from the rest of the organism.

After discovering these genes in actinomycetes and how they work, the investigators studied how widespread these genes are in other microorganisms. They were surprised to find that in addition to

actinomycetes, the genes were also present in several microorganisms commonly found in the human microbiota, the collection of microorganisms that naturally inhabit the human body.

"This raises a lot of questions that no one has ever asked before," Shen says. "I can rationalize why the producing organism would have these genes, because it needs to protect itself from its own metabolites. But why do other microorganisms need these resistance genes?" He notes that it may be possible for gut microbes to pass the products of these genes on to their host—humans—which could contribute to drug resistance.

"These findings raise the possibility that the human microbiota might impact the efficacy of enediyne-based drugs and should be taken into consideration when developing new chemotherapies," Shen says. "Future efforts to survey the human microbiome for resistance elements should be an important part of natural product-based drug discovery programs."

*Other authors of the study, "Resistance to Enediyne Antitumor Antibiotics by Sequestration," were Chin-Yuan Chang, Xiaohui Yan, Ivana Crnovcic, Thibault Annaval, Jeffrey D. Rudolf, Dong Yang and Hindra, of Scripps Research, George N. Phillips, Jr. of Rice University, and Changsoo Chang, Boguslaw Nocek, Gyorgy Babnigg and Andrzej Joachimiak of Argonne National Laboratory.*

*This research was funded by the National Institutes of Health (grants GM098248, GM109456, GM121060, GM094585, CA078747, GM115575 and CA204484) and the Department of Energy, Office of Biological and Environmental Research (grant DE-AC02-06CH11357).*

**Some existing anti-cancer drugs may act in part by targeting RNA, study shows**

JUPITER, FL – June 28, 2018 - Bolstering the notion that RNA should be considered an important drug-discovery target, scientists at Scripps Research have found that several existing, FDA-approved anti-cancer drugs may work, in part, by binding tightly to RNA, the regulators of the basic activities of life within cells.

The research offers another approach for tackling diseases that have been considered "undruggable," including amyotrophic lateral sclerosis (ALS), muscular dystrophy, cystic fibrosis and certain cancers.

"Known drugs made in the era when RNAs were not considered drug targets are, in fact, binding RNA, and causing some of the drug's effects by modulating targets that were not previously considered," says chemist Matthew D. Disney, PhD, professor on the Florida campus of Scripps Research, who led the study. "We found broad drug classes that bind RNA. There is reason to believe that not only could known drugs bind RNA in a disease setting, but there is more evidence that one should consider RNA as a target in drug-discovery efforts."

While the universe of human proteins consists of about 20,000 varieties, the universe of human RNAs is closer to 200,000, potentially offering other effective opportunities to intervene, Disney says.

The paper, "Approved Anti-Cancer Drugs Target Oncogenic Non-Coding RNAs," appears in the journal *Cell Chemical Biology* June 28.

Most drugs on the market today come in the form of pills that contain active small molecule medicines. Through a process called structure-based drug design, chemists optimize such small

molecule drugs to bind selectively and tightly to their biologic targets. The target is generally the pocket of a protein important in disease progression.

But there are limitations to small molecules. Because proteins are large and contain many folds and crevasses, sometimes key disease-driving areas are inaccessible to small molecule drugs. This problem has inspired Disney and other researchers to take a closer look at the roots of diseases. Because RNAs are involved in assembling proteins within cells, some have hypothesized that "undruggable" diseases could be modified prior to protein fabrication, at the RNA level.

Disney says he has encountered skepticism about the value of pursuing RNA-binding small molecule therapeutics. The thought was RNAs presented too challenging a target due to their size, movement, changeability and uncertain specificity. RNAs are shape-shifters, and generally thought to lack clearly defined structures to which a small molecule drug could obviously bind. Yet all along, as the new study shows, existing drugs have been doing just that—and binding defined pockets in an RNA—Disney says.

To explore his hypothesis, Disney devised a system for rapidly testing a large library of existing drugs against a wide variety of RNA molecules. He calls his testing system AbsorbArray.

"Basically, we figured out a way in which we could test millions of combinations of small molecule medicines and RNA folds that bind to each other," Disney says.

With AbsorbArray, the researchers identified the three drugs that bound to one type of microRNA and found they were microRNAs involved in every cancer. The drugs, called kinase- and topoisomerase-inhibitors, interfere with expression of a microRNA called miR-21. In further testing, it became clear that interfering with that microRNA prevented cancer cells from invading tissue.

"This data supports the hypothesis that very average-looking small molecule drugs can target RNA," Disney says.

Conducting the experiment required using a library of known small molecule drugs, and testing them against another library, of pre-messenger RNA, a process Disney called two-dimensional combinatorial screening. He was assisted in that effort by Arnab K. Chatterjee, PhD, at the California Institute for Biomedical Research (Calibr), a division of Scripps Research, which supplied the RNA splicing modulator library for the experiments.

"What is particularly interesting to me as a chemist is how existing compounds that have been tested in the clinic and optimized on one protein target may have additional novel activities in targeting RNA as well," Chatterjee says.

Looking forward, the next question is whether the selectivity and drug-like properties of these anti-cancer compounds will extend to diseases other than cancers, Chatterjee says.

In recent years, the Disney lab has found RNA-binding molecules applicable to many diseases, including ALS, myotonic dystrophy type 2, triple-negative breast cancer, inflammation, cystic fibrosis, Alport syndrome and more. The AbsorbArray findings underscore the likely value of continuing to move these disease-relevant RNA-binding compounds toward a clinical setting, Disney said.

"Drugs that patients take every day apparently target RNA, which is only recently being thought of as a target for small molecule medicines," Disney says. "As new RNAs are found to cause disease, routine medicines may be identified to target them. This would change the perception of RNAs as an afterthought in drug discovery and bring them to the forefront."

*Other authors of the study, "Approved Anti-Cancer Drugs Target Oncogenic Non-Coding RNAs," include Sai Pradeep Velagapudi, Matthew G. Costales, Balayeshwanth R. Vummidi, Yoshio Nakai, Alicia J. Angelbello, Tuan Tran, Hafeez S. Haniff, Yasumasa Matsumoto, Zi Fu Wang and Jessica L. Childs-Disney of Scripps Research and Arnab K. Chatterjee of the California Institute for Biomedical Research (CALIBR).*

*This work was supported by the Scheller Graduate Student Fellowship, a Swiss National Science Foundation Early Postdoc Mobility Fellowship, and the National Institutes of Health (grant 5R01GM097455).*

**Quest for safer pain-medications garners $3.6 million, five-year grant**

JUPITER, FL – August 17, 2018 - Researchers aim to control pain without the risk of addiction.

The National Institute on Drug Abuse, part of the National Institutes of Health, has awarded a five-year, $3.68 million grant to two Scripps Research scientists, Laura Bohn, PhD, and Thomas Bannister, PhD, to advance their work developing safer pain medications.

Previously, Bohn and Bannister, based in Jupiter, Florida, had developed new compounds that separate the powerful pain-relieving benefit of opioids from the life-threatening side-effect of decreased breathing rate and lower blood-oxygen levels. The new round of funding enables the team to further improve these compounds while also evaluating the extent to which other common opioid side effects, including constipation, drug tolerance, and especially addiction risk, are inherently altered in these new compounds, with an eye toward further widening the safety margins.

"We want to determine if these compounds produce drug preference, which is a sign of abuse potential, and to make new compounds that have built-in abuse deterrence — to control pain without the risk of addiction," Bohn says.

People who experience severe pain from cancer, car accidents, surgeries, burns and other traumas frequently require powerful pain relievers, sometimes for sustained periods. Because tolerance develops over time, their physicians often must increase dosage to maintain pain relief, raising the risk of overdose and addiction. New pain medications that diminish pain, minimize risk of overdose and other side effects, and also limit abuse potential, are sorely needed, Bohn says.

An expert in a cell-signaling system called G-protein-coupled receptors, Bohn worked many years with Bannister, a medicinal chemist, to develop compounds that activate a receptor called the mu opioid receptor, which relieves pain, without likewise activating the beta-arrestin pathway, associated with the harmful effects of pain killers. They published their findings in the journal *Cell*last year.

"Many leaders in the field of pain research have steered away from targeting the mu opioid receptor due to severe side-effects. Knowing that several of these effects can, in fact, be avoided is a finding that could offer hope to people who need effective but safe pain relief," Bannister says.

*The grant number is 2R01DA033073-06.*

**World-leading scientific research institute debuts new name and look**

LA JOLLA, CA & JUPITER, FL – August 27, 2018 - Under the leadership of noted chemist and CEO Peter Schultz, PhD, who is also a successful biotech entrepreneur, one of the largest private, nonprofit scientific research institutes in the world has undergone a rapid evolution in just three years. Its board of directors has been heavily revamped and populated with influential leaders of industry. Affiliations and mergers have expanded institute capabilities from basic research through drug discovery and development and into early clinical trials. Its Translational Institute, headed by pioneering physician-scientist and Executive Vice President Eric Topol, MD, uses genomics and digital tools to promote individualized medicine. And the organization is currently ranked the #1 nonprofit institute in the world for its influence on innovation as well as for its high-quality research by *Nature Index*.

To celebrate that evolution, the institute formerly known as The Scripps Research Institute has given itself an extensive makeover. On Aug. 1, leadership debuted a new name, a new logo and a new, more easily navigated website. Now known succinctly as Scripps Research, the bicoastal institute replaced its molecule-shaped logo with a sleek "infinity loop." According to its website, the new logo "represents our continual pursuit of knowledge and the infinite promise within science to improve health." The institute's new tag line, or slogan, captures the breadth and impact of its daily work: Science Changing Life.

"We have markedly broadened our scientific mission to include more applied, cutting-edge research to transform the future of medicine," says Topol. "Scripps Research is leading a major part of the national Precision Medicine Initiative, a million-participant program, and has been selected by the National Institutes of Health for its flagship Clinical and Translational Science Awards Program, with our most recent grant extending to 2023. Combined with the institute's long and outstanding track record in fundamental scientific research and drug discovery, we have a number of important stories to tell."

Anna-Marie Rooney, vice president of Communications at Scripps Research, says the rebranding process was an institute-wide effort. "From the start," she says, "we asked for input from every viewpoint—executive, administrator, student and scientist. We wanted the new message and imagery to demonstrate who we are and what we do. And the feedback kept returning to people. 'Make it human; show the profound connection we have with improving people's lives.' That's how we arrived at our tag: Science Changing Life." She says the process, which began only a few months ago, was successfully steered by a rising San Diego creative agency, Grizzly, who has worked with corporate giants such as Microsoft and Nestle. "I can't say enough about Grizzly's leadership and creativity," Rooney adds. "They knocked this project out of the ballpark."

Scripps Research performs biomedical research and drug discovery on two campuses, one in La Jolla, California and the other in Jupiter, Florida. Institute discoveries have led to nine approved drugs to date. In June, Scripps Research announced a licensing agreement with pharmaceutical company AbbVie to develop new cancer therapies based on an improved CAR-T platform technology developed within Calibr, the institute's drug discovery and development division. CAR-T therapy enlists a patient's own immune system to attack cancer cells. AbbVie currently markets *Humira*, the best-selling prescription drug in the world, which was also developed from discoveries at Scripps Research.