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**RESEARCH NEWS**

Team Determines How Antibiotic Gains Cancer-Killing Sulfur Atoms

In a discovery with implications for future drug design, scientists from the Florida campus of The Scripps Research Institute (TSRI) have revealed an unprecedented mechanism for how a natural antibiotic with antitumor properties incorporates sulfur into its molecular structure, an essential ingredient of its antitumor activity.

This new discovery could open the way to incorporating sulfur into other natural products, potentially advancing new therapies for indications beyond cancer.

The study, which was led by TSRI Professor Ben Shen, was recently released published by the journal *Proceedings of the National Academy of Sciences*.

“We found a novel mechanism to incorporate sulfur into natural products, which is unprecedented,” Shen said. “Until our study, we didn’t really know how sulfur atoms are incorporated into a natural product—now we have discovered a new family of enzymes and have a workable mechanism to account for sulfur incorporation into a larger class of natural products, known as polyketides, that include many drugs such as erythromycin (antibacterial) and lovastatin (cholesterol lowering).”

Scientists Uncover Surprising Mechanism Behind Antibiotic-Resistant Bacteria

Every year, more strains of bacteria develop resistance to the antibiotics we use to treat deadly infections. At TSRI, scientists have been working to develop new forms of these drugs, including an antibiotic called arylomycin—but tests have shown that it is possible for bacteria to become resistant to arylomycin, too.

Now, scientists at TSRI have discovered that the important human pathogen *Staphylococcus aureus*, develops resistance to this drug by “switching on” a previously uncharacterized set of genes.

“This explains why antibiotic resistance rates in some bacteria are higher than in others,” said TSRI Professor Floyd Romesberg, senior author of the new study in the journal *mBio*. “Resistance depends on this little set of genes that no one knew could contribute to tolerating the arylomycins.”

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Right: Floyd Romesbery, Arryn Craney
New Study Makes Major Advance Toward More Effective, Long-Lasting Flu Vaccine

Scientists from TSRI and the Janssen Pharmaceutical Companies of Johnson & Johnson have found a way to induce antibodies to fight a wide range of influenza subtypes—work that could one day eliminate the need for repeated seasonal flu shots.

“This study shows that we’re moving in the right direction for a universal flu vaccine,” said Ian Wilson, Hansen Professor of Structural Biology and chair of the Department of Integrative Structural and Computational Biology at TSRI.

The study published in *Science* was part of TSRI’s long-term collaboration to strengthen research against infectious disease with the former Crucell Vaccine Institute, now known as Janssen Prevention Center.

Chemists Report Nicotine-Chomping Bacteria May Hold Key to Anti-Smoking Therapy

A new study from TSRI scientists explores a bacterial enzyme that might be used as a drug candidate to help people quit smoking. The research shows that this enzyme can be recreated in lab settings and possesses a number of promising characteristics for drug development.

“Our research is in the early phase of drug development process, but the study tells us the enzyme has the right properties to eventually become a successful therapeutic,” said Kim Janda, the Ely R. Callaway Jr. Professor of Chemistry and member of the Skaggs Institute for Chemical Biology at TSRI.

The new research, published recently in the *Journal of the American Chemical Society*, offers a possible alternative to current smoking cessation aids, which are shown to fail in at least 80 to 90 percent of smokers. The idea behind an enzyme therapy would be to seek out and destroy nicotine before it reaches the brain—depriving a person of the “reward” of nicotine that can trigger relapse into smoking.

Researchers Make Strides in Preventing Relapse by Erasing Drug-Associated Memories

Recovering addicts often grapple with the ghosts of their addiction—memories that tempt them to relapse even after rehabilitation and months, or even years, of drug-free living.

Now, scientists from Scripps Florida have made a discovery that brings them closer to a new therapy based on selectively erasing these dangerous and tenacious drug-associated memories.

“We now have a viable target and by blocking that target, we can disrupt, and potentially erase, drug memories, leaving other memories intact,” said TSRI Associate Professor Courtney Miller.

“The hope is that, when combined with traditional rehabilitation and abstinence therapies, we can reduce or eliminate relapse for meth users after a single treatment by taking away the power of an individual’s triggers.”

The new study, published recently by the journal *Molecular Psychiatry*, demonstrates the effectiveness of a single injection of an early drug candidate called blebbistatin in preventing relapse in animal models of methamphetamine addiction.

Study Identifies Novel Role of Mitochondria in Immune Function

TSRI scientists have discovered a new role for an enzyme involved in cell death. Their study shows how the enzyme, called RIPK3, relays signals between the cell’s mitochondria “powerhouses” and the immune system.

The new study in the journal *Nature Communications* shows that this crosstalk is important not only for launching immune responses against tumors, but also for regulating the inflammatory responses that may result in autoimmune diseases.

“This finding could be helpful for developing strategies to target cancer and inflammatory diseases,” said TSRI Assistant Professor of Immunology Young Jun Kang, who collaborated on the study.
Structural Discoveries Could Aid in Better Drug Design

F. Scott Fitzgerald once said that the test of a first-rate intelligence is the ability to hold two opposed ideas in mind at the same time and still retain the ability to function. Now, scientists from Scripps Florida have found the biological equivalent of that idea or something very close.

For the first time, they have uncovered the structural details of how some proteins interact to turn two different signals into a single integrated output. These new findings could aid future drug design by giving scientists an edge in fine tuning the signal between these partnered proteins—and the drug’s course of action.

“Thyroid, vitamin D and retinoid receptors all rely on integrated signals—their own signal plus a partner receptor,” said TSRI Associate Professor Kendall Nettles, who led the Nature Communications study with TSRI colleague Associate Professor Douglas Kojetin. “These new findings will have important implications for drug design by clearly defining exactly how these signals become integrated, so we will be able to predict how changes in a drug’s design could affect signaling.”

Scientists Identify a Key Morphine Regulator that May Reduce Risk of Pain-Killer Abuse and Addiction

Once used in the 18th century as currency to reverse the trade imbalance between China and Britain, morphine and its pain-killing qualities have been misunderstood (and misused) almost continually ever since.

The drug works its euphoric effect by acting on a specific protein that has been part of vertebrate anatomy for nearly a half-billion years. Despite that lengthy pedigree, regulation of these receptor proteins has never been well understood.

A new study in Biological Psychiatry led by Kirill Martemyanov, an associate professor on the Scripps Florida campus, has shown that a specific molecule controls morphine receptor signaling in a small group of brain cells. The findings could lead to a new drug target for developing less-addictive pain medications and even offer a clue to the genetic predisposition of patients to addiction before treatment.

TSRI and UC San Diego Launch Consortium to Create ‘Virtual Cell’

Drawing on complementary strengths of two San Diego institutions, The Scripps Research Institute (TSRI) and the University of California, San Diego (UC San Diego) have formed a new consortium with a big mission: to map cells in space and time. The work will lay important groundwork to understanding health and disease.

“Even the simplest living cells contain 1 to 2 million proteins of 3,000 to 4,000 different types,” said TSRI Professor Art Olson, who will co-direct the project with UC San Diego Associate Professor of Chemistry and Biochemistry Rommie Amaro. “Figuring out how they work together over time will shed light on the cell as a living, working individual entity. Just like you couldn’t build a car from just its wiring diagram, we can’t have a complete understanding of a cell unless we know how all of its physical parts work together in 3D.”

The Visible Molecular Cell Consortium (VMCC) will offer fellowship funding for some 10 to 12 graduate students and postdoctoral fellows to work on collaborative projects that build bridges between the campuses and different disciplines to assemble and simulate a virtual model of a cell, down to an atomic level of detail.
The Scripps Research Institute (TSRI) has announced the appointment of chemist Peter G. Schultz as CEO and biologist Steve A. Kay as president-elect, effective immediately.

Schultz is currently a member of the TSRI faculty, as well as director of the California Institute for Biomedical Research (Calibr). He is also a successful entrepreneur and has led major drug discovery efforts in both the commercial and nonprofit sectors.

Kay, a former TSRI faculty member, is currently dean of the Dornsife College of Letters, Arts and Sciences at the University of Southern California (USC). His work has been highlighted in Science magazine’s “Breakthroughs of the Year” on three separate occasions.

“I am delighted that Pete and Steve will assume leadership roles at TSRI,” said Chair of the TSRI Board of Trustees and President/CEO of Gephardt Government Affairs Dick Gephardt. “Their shared vision of creating a unique position for the institute at the forefront of basic and translational research is tremendously exciting. I expect great things to come.”

“After 16 years on the faculty, I am delighted with the opportunity to give back to the institute in a leadership role,” said Schultz. “I have a tremendous respect for TSRI’s commitment to scientific excellence and the collegiality and entrepreneurial spirit of the faculty. These qualities are key as we move forward into a new era of biomedical research in which TSRI will play a leadership role. There is a lot to be done, and I look forward to working with Steve, the Board, faculty and staff as a team to further expand the footprint of Scripps in science and medicine.”

“I welcome the opportunity to return to Scripps,” said Kay, “and to realize a vision of combining the institute’s world-class reputation in basic biological and chemical sciences with the ability to advance novel therapeutics for major unmet medical needs. I look forward to working together with Pete and TSRI’s board, faculty, staff, administration, postdocs, students, friends and donors to enhance the institute’s contributions to biomedical research, graduate education and human health.”

Gephardt noted that Schultz will take the lead in developing long-term strategy and external alliances, with a focus on building “bench-to-bedside” research capabilities, while Kay will spearhead the academic and operational activities of the institute. Schultz and Kay will work together to further enhance the institute’s scientific reputation and build a strong financial base.

Gephardt expressed his gratitude to James Paulson, who has been acting president and CEO since August 2014. “Jim has served the institute admirably during this transition, and I would like to extend my deepest thanks for his meaningful leadership during this critical transition.”

“I expect great things to come,” says Chair of the TSRI Board of Trustees Dick Gephardt (left), of the new leadership team, CEO Peter Schultz (right) and President-Elect Steve Kay.
CEO and Vice Chair: Peter G. Schultz

Peter Schultz graduated from Caltech with a B.S. in Chemistry and continued there for his doctoral degree in 1984. After a postdoctoral year at the Massachusetts Institute of Technology, he moved to the University of California, Berkeley, where he was a professor of chemistry, a principal investigator at the Lawrence Berkeley National Laboratory and an investigator in the Howard Hughes Medical Institute. He moved to TSRI in 1999, where he is currently the Scripps Family Chair Professor of Chemistry.

Schultz’s research is at the interface of chemistry and biology. He has pioneered technologies to make and characterize molecules and materials hundreds to millions at a time—work that has dramatically impacted our ability to create new medicines and materials. He has led the development of new drugs that affect endogenous stem cells for neurodegenerative diseases and diseases of aging, and has directed efforts that have resulted in breakthrough therapies for the treatment of cancer, autoimmune and infectious disease. Most recently his laboratory has successfully created new “synthetic” organisms in which the evolutionary constraints of the 20-amino acid genetic code are lifted, allowing scientists to create biomolecules with new activities that are not possible using Mother Nature’s code.

Schultz has coauthored roughly 600 scientific publications and trained more than 300 coworkers, many of whom are on the faculties of major institutions throughout the world. He is a founder of nine biotech/tech companies that have pioneered the development and application of new technologies to challenges in energy, materials and human health. In 1999 he founded the Genomics Institute of the Novartis Research Foundation (GNF), one of the world’s leading translational research institutes, and in 2012 he formed the nonprofit biomedical research institute Calibr as a new model to accelerate the discovery of medicines for unmet needs.

Schultz has received numerous awards including the National Science Foundation (1988), the American Chemical Society (ACS) Award in Pure Chemistry (1990), the Wolf Prize in Chemistry (1994), Alan T. Waterman Award (1998), the Paul Erhlich and Ludwig Darmstaedter Award (2002), the ACS Arthur C. Cope Award (2006) and the Solvay Prize (2013). He is a member of the National Academy of Sciences, USA (1993) and the Institute of Medicine of the National Academy of Sciences (1998).

President: Steve A. Kay

Steve A. Kay, a graduate of the University of Bristol, United Kingdom (BSc, 1981; PhD, 1984; DSc, 2014), conducted postdoctoral work at The Rockefeller University with Professor Nam-Hai Chua. He was subsequently appointed a member of the faculty at Rockefeller and then joined the University of Virginia in 1992.

In 1996, he moved to TSRI, where he rose to become professor in the Department of Cell Biology, chairman of the Department of Biochemistry, director of the Institute for Childhood and Neglected Diseases and chairman of the Scripps Florida Steering Committee. During this time (1999-2004), he was also director of discovery research at GNF, where he helped build research programs applying human genome science to biomedical research and drug discovery.

In 2007, Kay joined the University of California (UC), San Diego, where he was dean of biological sciences and Richard C. Atkinson Chair in Biological Sciences. In 2012, he joined USC as dean of Dornsife College, also holding the Anna H. Bing Dean’s Chair. While at USC, Kay was responsible for building large-scale academic programs and was widely recognized for prolific fundraising to support his vision.

An internationally renowned expert on genes and circadian rhythms, Kay has published more than 250 papers and was recently named by Thomson Reuters as a Highly Cited Researcher. He was elected a member of the National Academy of Sciences in 2008 and a fellow of the American Association for the Advancement of Science in 2009. In 2010, he was awarded the UC San Diego Chancellor’s Associates Faculty Award for Excellence in Research. In recognition of his pioneering work in plant sciences, Kay was chosen to receive the 2011 Martin Gibbs Medal by the American Society for Plant Biology.

Kay also has founded several biotechnology companies, most recently Reset Therapeutics, a San Francisco-based drug development corporation.
Scripps Research Institute Receives $5.65 Million Gift from San Diego Philanthropist Helen Dorris

The Scripps Research Institute (TSRI) has received a $5.65 million gift from Helen Dorris, a San Diego mental health advocate and founder of TSRI’s Dorris Neuroscience Center.

“We are deeply grateful to Helen Dorris and her continued generosity in the support of neuroscience research at TSRI,” said James Paulson, acting president and CEO at the time of the announcement. “Her gifts help make possible discoveries that deepen our understanding of the nervous system and underscores her belief that neuroscience is at the threshold of advancing new treatments for devastating neurological conditions.”

“Thanks to Helen Dorris’s generosity, we have made progress finding new approaches to diseases from hearing loss and pain to hydrocephalus, schizophrenia and Alzheimer’s,” said Ulrich Mueller, director of the Dorris Neuroscience Center. “The new gift ensures we will continue to forge new ground.”

Dorris, who is a San Diego State University professor emeritus, founded a neuroscience center at TSRI in 1999 with a commitment of $10 million. The center was originally named the Harold L. Dorris Neurological Research Center, in her brother’s honor. She later founded TSRI’s Helen L. Dorris Institute for the Study of Neu- rological and Psychiatric Disorders of Children and Adolescents. The two centers were consolidated in 2010 with an additional gift through The Harold L. Dorris Neuroscience Foundation.

The new gift will enhance the established endowment for the Dorris Neuroscience Center.

The Dorris Neuroscience Center brings together scientists early in their careers with established researchers in the field and provides them with high-end imaging technology and state-of-the-art genomic and genetic research tools to advance their research.

Using diverse interdisciplinary biological, biophysical and chemical approaches, the researchers conduct investigations with particular strengths in sensory systems (including smell, hearing and pain), neuronal circuitry (including the systems that govern memory) and stem cell research. Many of these laboratories are located in the Harold L. Dorris Neuroscience Center Building, a 53,000-square-foot structure with cutting-edge facilities for imaging and behavior studies.

The Dorris Neuroscience Center also sponsors three Helen Dorris Scholars, an annual student award, a number of summer student internships and a distinguished lecture series.
Scientists Awarded $6 Million to Develop Alternative HIV/AIDS Vaccine

Scripps Florida scientists have been awarded up to nearly $6 million dollars from the Bill & Melinda Gates Foundation to develop a revolutionary HIV/AIDS alternative vaccine that has demonstrated great potential in animal models.

The research, to be led by TSRI Professor Michael Farzan, will be supported by four years of funding—the first grant awarded by the Gates Foundation to a Scripps Florida scientist.

“I’m grateful to the Gates Foundation for its strong support of our research and for its continued commitment to eradicating HIV/AIDS throughout the world,” Farzan said.

Farzan brings an innovative approach to combating HIV. The approach works by coaxing muscle cells into producing inhibitor proteins that block key sites on the virus’s surface used to attach and invade human immune cells—fooling the virus into thinking it is binding to a human cell.

Unable to attach to cells, and unable to reproduce, the virus simply floats impotently in the bloodstream.

Farzan and colleagues’ breakthrough research received worldwide attention when announced earlier this year in the journal *Nature*. When the drug candidate, called eCD4-lg, was tested in the laboratory and in animal models, the results were so powerful and universally effective that they suggested the compound’s potential to serve the role of an alternative HIV/AIDS vaccine. The drug candidate offered complete protection of animal models against the virus for up to one year.

“At the end of our research, we expect to have enough evidence to develop a firm foundation to fully evaluate its potential as an alternative vaccine,” Farzan said.

There are approximately 35 million people living with HIV-1—more than 25 million in sub-Saharan Africa—and more than two million new infections annually.

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GIVING

This Year Make a Tribute Gift and Make a Difference to Medical Research

Now is your opportunity to honor a loved one or a dear friend by making a charitable gift before year end. Simply visit our website at www.scripps.edu/philanthropy and click on the *Donate Now* button. Your tribute gift will benefit not only those you honor but also medical research at The Scripps Research Institute (TSRI) – including research programs tackling many dreaded diseases such as cancer, diabetes, Alzheimer’s, Parkinson’s, Ebola and more.

If you’d like to learn more about other ways to make a tribute gift to TSRI, visit our planned giving website... Discover the Benefits of Giving Wisely at www.plannedgiving.scripps.edu. There you will find ideas and information to support our world class research including estate and charitable planning; tax deduction calculators for charitable gifts; and inspirational stories of people like you who have supported TSRI with charitable planning.

Of course, if you would like to contact us directly, we would be happy to help assist you maximize your charitable and financial goals. For more information about your giving options, please contact Geoff Graham, director, planned giving and estates, at (858) 784-9365 or gcgraham@scripps.edu. In Florida, contact Irv Geffen, director of philanthropy, at (561) 228-2017 or igeffen@scripps.edu.

When considering charitable gifts you are urged to seek the advice of your own financial and legal advisor(s) about your specific situation.
New ‘Innovation Indicator’ Ranks TSRI Number One

A new “innovation indicator” put out recently by The Times of Higher Education in collaboration with Elsevier ranks TSRI number one in the world as measured by the proportion of papers cited by patents. The analysis spanned the “STEMM fields” of science, technology, engineering, medicine and mathematics.

Nature Reviews Highlights Sale of TSRI Spin-Off Developing MS, Ulcerative Colitis Drug Candidate

A recent article in Nature Reviews Drug Discovery highlights the sale of Receptos, a biotech company founded by licensing patents from TSRI, to global biopharmaceutical company Celgene for $7.3 billion.

The drug candidate, called ozanimod (previously known as RPC1063), was first discovered and synthesized in the Scripps California laboratories of Professors Hugh Rosen and Ed Roberts, based on a hit from the Scripps Florida Molecular Screening Center, which was part of the National Institutes of Health (NIH) Molecular Libraries Program. Ozanimod is now in two separate Phase III trials for treatment of relapsing-remitting multiple sclerosis and ulcerative colitis, and in a Phase II trial for Crohn’s disease.

“Ozanimod is the first and most advanced compound to emerge from the NIH Common Fund efforts thus far and is an important illustration of the impact of TSRI’s unique faculty environment and infrastructure integrating deep biological and chemical insights,” Rosen said. “These strengths together with an entrepreneurial vision and flawless execution improve the lives and dignity of patients and families dealing with disabling and debilitating diseases.”

Sathya Puthanveettil Receives NSF CAREER Award

Sathya Puthanveettil, associate professor of neuroscience at Scripps Florida, has received a Faculty Early Career Development (CAREER) award from the National Science Foundation (NSF). The grant is the foundation’s most prestigious award in support of junior faculty who exemplify the role of teacher-scholar through outstanding research, excellent education and the integration of education and research within the context of the mission of their organization.

The CAREER award is based on Puthanveettil’s project, “Molecular Basis of Synapse Specific Long-Term Memory Storage,” which aims to bring novel molecular and mechanistic insights to the understanding of long-term memory storage. The project focuses on identifying and characterizing spatial-temporal changes in mRNAs localized to specific synaptic compartments for storing long-term memories.
Scientists Win $4.5 Million to Complete Preclinical Trials for New Migraine Treatment

TSRI scientists have received a grant of nearly $4.5 million—with the possibility of up to $10 million including outsourced studies—from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH) to complete preclinical studies on a new anti-migraine drug candidate.

“Migraine is the world’s most common neurological disorder, and the number one trigger for migraine is stress,” said TSRI Professor Ed Roberts, who will direct the project with TSRI Professor Hugh Rosen, a long-time colleague and collaborator.

This new research program has its roots in primary “hit” molecules identified at the TSRI Molecular Screening Center at Scripps Florida, while supported by the NIH Molecular Libraries Program. This “hit” underwent a rigorous optimization process in the Scripps California laboratories of Roberts and Rosen. Intriguingly, the new drug candidate acts on protein targets that are intimately involved with the body’s stress mechanisms. This activity led the researchers to consider it as a treatment for stress-induced migraine.

Film Screening Sparks Discussion About Parkinson’s Research

A screening of the documentary film, “It Seems Like Magic ... But It’s Science - A Quest to End Parkinson’s Disease” attracted 150 participants to the TSRI Auditorium in July. The film featured the inspirational story of how 10 people trekked to Mt. Everest to raise funds and awareness for non-embryonic stem cell research at TSRI.

Following the screening, a panel discussion featured scientists, physicians and hikers, including: physician Melissa Houser, founder and clinical director of the Parkinson’s Disease and Movement Disorder Center at Scripps Clinic; Sherrie Gould, nurse practitioner and creator of the nonprofit organization, Summit4stemcell; Jeanne Loring, professor of developmental neurobiology at TSRI; and Andres Bratt-Leal, TSRI research associate and senior research scientist at the Parkinson’s Association of San Diego.

Panelists Melissa Houser, Sherrie Gould, Jeanne Loring and Andres Bratt-Leal shared their thoughts on the critical nature of stem cell research to treat Parkinson’s.

EVENTS
Matthew D. Disney, a professor on the Florida campus of The Scripps Research Institute (TSRI), has been awarded a prestigious 2015 Pioneer Award from the National Institutes of Health (NIH). The award, one of only 13 given this year, enables scientists to develop groundbreaking approaches with a significant impact on broad areas of biomedical science.

“This program has consistently produced research that revolutionized scientific fields by giving investigators the freedom to take risks and explore potentially ground-breaking concepts,” said NIH Director Francis S. Collins. “We look forward to the remarkable advances in biomedical research the 2015 awardees will make.”

The Pioneer Award, established in 2004, is part of the NIH’s High-Risk, High-Reward Research program supported by the NIH Common Fund designated for scientists of “exceptional creativity.” Disney’s Pioneer Award provides $4.8 million of funding over five years.

“We will use the money wisely to advance precision therapeutics that trick disease-affected cells into making their own drug against diseases for which there are no known cures,” said Disney.

His approach will be applied towards more than 30 incurable diseases, including amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig disease), fragile X syndrome (the most common cause of autism) and Huntington’s disease.

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

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