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Scientists from The Scripps Research Institute’s (TSRI) Florida campus have for the first time discovered a killing mechanism that could underpin a range of the most intractable neurodegenerative diseases such as Alzheimer’s, Parkinson’s and ALS.

The new study, published recently in the journal *Brain*, revealed the mechanism of toxicity of a misfolded form of the protein that underlies prion diseases, such as bovine spongiform encephalopathy (“mad cow disease”) and its human equivalent, Creutzfeldt-Jakob disease.

“Our study reveals a novel mechanism of neuronal death involved in a neurodegenerative protein-misfolding disease,” said Corinne Lasmézas, a TSRI professor who led the study. “Importantly, the death of these cells is preventable. In our study, ailing neurons in culture and in an animal model were completely rescued by treatment, despite the continued presence of the toxic misfolded protein. This work suggests treatment strategies for prion diseases—and possibly other protein misfolding diseases such as Alzheimer’s.”

A team led by scientists at TSRI and Johns Hopkins University School of Medicine has uncovered a big clue as to how bacteria may promote some colon cancers.

The study, reported recently in *Cell Metabolism*, used novel metabolomic technologies to reveal molecular evidence suggesting a vicious circle in which cancerous changes in colon cells promote the growth of bacterial conglomerations called biofilms, and biofilms in turn promote cancer development.

On the whole, the findings suggest that removing bacterial biofilms could be a key strategy for preventing and treating colon cancers, which currently kill about 50,000 Americans per year. The study also revealed an apparent metabolic marker of biofilm-associated colon cancers.

The research, which used sophisticated “metabolomics” techniques, was a collaboration between groups, including the team led by Gary Siuzdak, professor of chemistry, molecular and computational biology and senior director of the Scripps Center for Metabolomics at TSRI.
Scientists Confirm Key Targets of New Anti-Cancer Drug Candidates

Ribosomes, ancient molecular machines that produce proteins in cells, are required for cell growth in all organisms, accomplishing strikingly complex tasks with apparent ease. But defects in the assembly process and its regulation can lead to serious biological problems, including cancer.

Now, in a study published recently in *The Journal of Cell Biology*, scientists from the Florida campus of TSRI have confirmed the ribosome assembly process as a potentially fertile new target for anti-cancer drugs by detailing the essential function of a key component in the assembly process.

“This study confirms that ribosome assembly is a good therapeutic target in cancer,” said Katrin Karbstein, a TSRI associate professor who led the study. “Whether or not we have pinpointed the best molecule remains to be shown, but this is a vindication of our basic research. There should be effort devoted to exploring this pathway.”

Team Uncovers How Molecule Protects Brain Cells in Parkinson’s Disease Model

Scientists from TSRI’s Florida campus have found how a widely known but little-studied enzyme protects brain cells in models of Parkinson’s disease.

These findings could provide valuable insight into the development of drug candidates that could protect brain cells in Parkinson’s and other neurodegenerative diseases.

The study, published recently by the journal *Molecular and Cellular Biology*, focuses on the enzyme known as serum glucocorticoid kinase 1 (SGK1).

“The overexpression of SGK1 provides neuron protection in both cell culture and in animal models,” said Philip LoGrasso, a TSRI professor who led the study. “It decreases reactive oxygen species generation and alleviates mitochondrial dysfunction.”

Using a neurotoxin animal model of neurodegeneration, the study showed that SGK1 protects brain cells by blocking several pathways involved in neurodegeneration, deactivating other molecules known as JNK, GSK3β and MKK4.

New Compound Prevents Type 1 Diabetes in Animal Models—Before It Begins

Scientists from the Florida campus of TSRI have successfully tested a potent synthetic compound that prevents type 1 diabetes in animal models of the disease.

“The animals in our study never developed high blood sugar indicative of diabetes, and beta cell damage was significantly reduced compared to animals that hadn’t been treated with our compound,” said Laura Solt, a TSRI biologist who led the study.

Type 1 diabetes is a consequence of the autoimmune destruction of insulin-producing beta cells in the pancreas. While standard treatment for the disease aims to replace lost insulin, the new study focuses instead on the possibility of preventing the initial devastation caused by the immune system—stopping the disease before it even gets started.

Researchers Connect Haywire Protein to Breast Cancer, Leukemia

A new study led by TSRI scientists sheds light on the cause of some cancers, including breast cancer and leukemia.

In the new study, published in *Current Biology*, the researchers found that too much of a key protein, called cyclin E, slows
down DNA replication and introduces potentially harmful cancer-linked mutations when cells divide.

“Overexpression of cyclin E is one route to cancer,” said TSRI Professor Steven Reed, senior author of the new study.

Research Reveals Surprising New Details of Potential Alzheimer’s Treatment
Taking a new approach, scientists from TSRI’s Florida campus have uncovered some surprising details of a group of compounds that have shown significant potential in stimulating the growth of brain cells and memory restoration in animal models that mimic Alzheimer’s disease.

The new study points to promising new directions using a known therapeutic strategy for Alzheimer’s disease—a disorder that will affect nearly 14 million Americans by 2050, according to the Alzheimer’s Association.

The study, which was led by TSRI Associate Professors Courtney Miller and Gavin Rumbaugh, appeared in the journal *Neuropsychopharmacology*.

This new study builds on previous findings from Miller and Rumbaugh demonstrating the memory-rescuing potential of inhibiting histone deacetylases (HDACs), a family of signaling enzymes that act like molecular switches, silencing gene expression by controlling access to the cell’s nuclear cache of tightly compacted DNA. Mutations in HDACs genes have been associated with health problems including cancer, inflammatory and autoimmune diseases, metabolic disorders and loss of memory function.

Scientists Find Clues to Cancer Drug Failure
Cancer patients fear the possibility that one day their cells might start rendering many different chemotherapy regimens ineffective. This phenomenon, called multidrug resistance, leads to tumors that defy treatment.

Now scientists at TSRI have published a pair of studies in *Structure* and *Acta Crystallographica Section D* showing how the primary protein responsible for multidrug chemotherapy resistance changes shape and reacts to therapeutic drugs.

“This information will help us design better molecules to inhibit or evade multidrug resistance,” said TSRI Associate Professor Qinghai Zhang, a senior author of both studies.

GIVING
Create a Lasting Tribute
Each and every day we receive tribute gifts...some are for loved ones and some are for dear friends...all gifts bring comfort in knowing that the tribute provides critical support through the advancement of medical research here at The Scripps Research Institute – in areas like cancer, Alzheimer’s disease, diabetes, heart disease, and Parkinson’s disease, to name a few.

Some of our supporters also find comfort and security by making a lasting tribute in the form of a charitable gift annuity – a type of gift that gives back to you income every quarter – creating a reminder of your tribute and your dedication to scientific research.

Here’s how this gift works...A charitable gift annuity is a contract between you and The Scripps Research Institute. You make a gift of cash or appreciated securities and in return TSRI provides to you an annuity for the rest of your life. These payments never decrease in size or frequency, regardless of the changes in the economy. Other benefits may include: an income tax deduction for a portion of your charitable gift; partial tax-free payments from federal income tax for a period of time; capital gains tax savings; estate taxes generally not due on amounts used to fund your annuity; and payments that could also benefit loved ones and friends.

For our more senior supporters, a charitable gift annuity is a smart way to create a lasting tribute to a friend or family member and invest for your future.

There are many ways in which a charitable gift annuity will work for you and a loved one. For more information or a confidential illustration, please contact Geoff Graham, director, planned giving and estates, at (858) 784-9365 or ggraham@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.
Herb and Barbara Shear have been committed philanthropists and have been active in the Pittsburgh community for years. They are currently in transition to becoming Palm Beach residents, and their interest in breast cancer has led them to support the research of Scripps Florida scientists Derek Duckett and William Roush.

Through the support of the Shears, Drs. Duckett and Roush are advancing the development of a breakthrough treatment for patients suffering from advanced breast cancer. The two scientists and their colleagues have used bioinformatics tools and medicinal chemistry, biochemistry, and cell biology approaches to optimize their research toward a potent breast cancer therapy that has selectively killed tumor cells in animal models. They are next taking the compound to Stage 1 trials.

“We’re pleased with and have been impressed with the results of the research thus far,” said Herb. It looks like the promising compound will have an impact and we’re looking forward to the next stage of trials.”

“We would like to sincerely thank the Shears for their generosity and passion to find a cure for advanced breast cancer,” said Dr. Duckett. “It has been a very productive and exciting collaboration.”

Herb is one of the Pittsburgh region’s truly accomplished business leaders and has earned an international reputation as a pioneer in the field of reverse logistics. He served for many years as chair and CEO of GENCO. Under Herb’s leadership, the firm experienced remarkable successes. After succeeding his father, Samuel Shear, as president of GENCO in 1971, he grew the family business into North America’s second-largest third-party logistics provider.

In terms of their philanthropy, Herb and Barbara have a few particular passions. “We’re mostly focused on medical research, hunger, and Jewish causes, including having an impact on Israeli infrastructure and society,” said Herb.

Herb is a trustee of the University of Pittsburgh and Barbara received her Masters of Education from Pitt in 1973. They are committed advocates and loyal supporters of the university, and have created, with their sons, the Shear Family Scholarship in the School of Pharmacy to honor Herb’s father. They have also generously supported the university through medical research projects in individualized medicine, gene sequencing, and Alzheimer’s disease.

An emeritus board member and past president of the Greater Pittsburgh Food Bank, Herb and Barbara where honored with the Individual Financial Donor Award during the food bank’s 20th anniversary.
celebration in 2001. Herb is a past chair of the Food Bank. Barbara currently serves on the Financial Committee of The Friendship Circle, a program that connects special needs children with teenagers in Pittsburgh. Herb is also affiliated with Leket: The National Food Bank of Israel.

Herb and Barbara have served as Honorary Chairs of the Jewish Family and Children’s Service Dinners in the Pittsburgh area and have contributed philanthropically to this organization. They are also committed members of the America Israel Public Affairs Committee and Barbara is a member of AIPAC National Council. Barbara is a member of the Board of Governors of Hebrew Union College – Jewish Institute of Religion. She is an active participant in the Jewish National Fund in both Pittsburgh and South Florida, and, in 2006, the Pittsburgh branch honored her for her efforts.

Outside of Pittsburgh and Florida, Herb earned his Bachelors of Science in marketing and finance from Southern Illinois University in 1969 and has received the university’s Distinguished Service Award thanks to his history of supporting his alma mater. Herb and Barbara provided a major leadership gift to raise the profile of the university’s College of Business and Administration and additional support for endowed professorships, computers for professors, and an MBA classroom.

Herb and Barbara are currently taking the proceeds from the recent sale of GENCO and establishing a foundation with their two sons, who are following in their parents’ footsteps in terms of their philanthropy.

“We hope that, through the foundation, we’ll have even more of an impact with our giving than in the past,” said Herb.

Herb and Barbara Shear are outstanding and caring individuals who are committed to moving their many important causes forward. ♦

“We would like to sincerely thank the Shears for their generosity and passion to find a cure for advanced breast cancer,” says Associate Professor Derek Duckett (center).

“We’re pleased with and have been impressed with the results of the research thus far.”

Herb Shear
How has your background at TSRI and elsewhere positioned you to discover new drugs?

I joined TSRI in 2006. Prior to coming here, I had an unconventional career compared to most academicians, as I was head of a laboratory in the biopharmaceutical industry for six years at the Genomics Institute of the Novartis Research Foundation (GNF). In that setting, I gained experience in drug discovery and in the validation of new drug targets. Through this experience, I further developed my commitment to improve people’s lives and cure disease.

At TSRI, I have a small and passionate group (four talented and hard working PhD scientists), and we focus every day on effectively addressing the best questions out there. Part of the reason we are able to deliver is also that TSRI lacks bureaucracy and allows us to focus on our research with minimal other obligations.

My previous experience, together with the synergistic and collaborative scientific and entrepreneurial environment at TSRI and the San Diego area as a whole, makes us uniquely positioned to turn the results of our research into new therapies for neurodegenerative diseases.

Tell us about your research, the diseases it impacts, and any breakthroughs.

We focus on elucidating how defects in protein quality control lead to neurodegenerative diseases. In particular we study a family of enzymes known as the E3 ubiquitin. Among other roles, E3 ligases help cells get rid of unwanted abnormal proteins. We know that cellular “garbage disposal” processes are important because the failure to eliminate aberrant proteins leading to their accumulation can have toxic consequences underlying several diseases.

We have made an exciting new discovery on amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease. We had previously found that mutation of a particular E3 ubiquitin ligase leads to symptoms similar to ALS in mice. Next, we found that this ligase participates in a new mechanism of protein quality control.

We then followed this up by collaborating with clinicians to translate our basic research results into new therapeutically relevant discoveries, and recently made a finding on mutations affecting this protein quality-control mechanism in human ALS patients. ALS researchers have already discovered several genes mutated in the disease, but the function of most of those genes has remained unknown. Our discovery presents an entire process that becomes affected, so this could serve as a framework to understand how mutations in those previously known genes lead to the disease.

The implications of these studies could extend well beyond ALS, as we believe that neurodegenerative diseases have much more in common among themselves than is currently recognized. For example, all neurodegenerative diseases are characterized by clumps of abnormal proteins that are not properly disposed of. Also, we know that mutations in the same gene are found in different diseases like Ataxin-2 (ALS and spinocerebellar ataxia) and TARDBP (ALS and a type of dementia).
How can private philanthropy help your lab? Tell us about your involvement in philanthropy for TSRI as a whole.

Obtaining research funds is very difficult these days. National Institutes of Health (NIH) funding has been decreasing and the lack of available cash limits our ability to move our discoveries to applications in the shortest possible time. That, and NIH funding tends to reward more conservative approaches, whereas philanthropic support allows scientists to take more risks. And we know that breakthroughs tend to come most often from high-risk approaches.

Our recent ALS breakthrough creates the opportunity for new therapeutic strategies and we’re putting together an ALS funding initiative to help translate our research findings into the development of promising new therapies. We need funding for staffing and for research reagents to answer tough questions. It would mean a lot to us and, we expect, ultimately to patients suffering from ALS.

I also am part of a new faculty philanthropy committee, which is helping to expose philanthropists to the great science at TSRI. This was my motivation recently in helping TSRI Acting President and CEO Jim Paulson and Director of Philanthropy Chris Lee bring philanthropists to a “Day at TSRI” through the Cavendish Global Health Impact Forum to showcase our science.

I understand you’re from Brazil and still visit frequently?

Yes, I grew up in a provincial town in Brazil and attended high school there. At the time, it was not common for people from those areas to leave in order to obtain a college education elsewhere, but by then I was already in love with science and the best Biology undergraduate program in the country was in São Paulo, so I moved there to pursue my studies. I was one of only two students from my high school class to go to college out of state, and the only one among 38 cousins to do so. As an undergraduate student at the University of São Paulo, I also joined a laboratory to work on the then-newly discovered “oncogenes” (cancer genes). After obtaining both my Bachelor’s and Master’s degrees there, I came to San Diego in 1990 for Ph.D. studies at UCSD, where great work on oncogenes and gene regulation was being done.

Through my trips back to Brazil, I’m trying to help develop the country’s biotechnology sector. My goal is to stimulate the Brazilian economy to become more knowledge-based, inspired by the economic growth I have witnessed over the last 25 years in San Diego as a result of biotech and high tech development.

You’ve been at TSRI for some time now. What do you think of the current state of affairs at the institute?

I’m very encouraged by the institute’s current direction. TSRI is becoming more inclusive of the faculty and of employees in general, and the criteria for making critical decisions are becoming more even across departments. As a result, the institute is becoming an even more exciting place to work.
Skaggs Family Renews Its Support for TSRI Research

TSRI’s most generous donor—the Skaggs family—has renewed its support of the institute with a $207,000 gift through The ALSAM Foundation.

“I would like to express my deep appreciation for the ALSAM Foundation contribution,” said Jim Paulson, TSRI’s acting president and CEO. “I am delighted that members of the ALSAM grants committee—including TSRI Trustees Claudia Skaggs Luttrell and Mark Skaggs—are continuing to demonstrate their far-sighted commitment to improving human health through biomedical science.”

The new donation will support the training of graduate students and postdoctoral fellows in the laboratories of TSRI Professors Kim Janda and Jeffery Kelly.

The gift follows presentations by Janda, Ely R. Callaway, Jr. Professor of Chemistry and Skaggs Scholar at The Skaggs Institute for Chemical Biology at TSRI, and Kelly, Lita Annenberg Hazen Professor of Chemistry and chair of TSRI’s Department of Molecular and Experimental Medicine, at the L.S. Skaggs Biomedical Research Symposium last year in Missoula, Montana.

The ALSAM Foundation is named in honor of the late philanthropist and entrepreneur L.S. “Sam” Skaggs Jr. and his wife, Aline. The foundation supports a variety of causes and organizations and is committed to improving the lives of people around the world.

Srini Subramaniam Wins Alzheimer’s Association Grant

Srini Subramaniam, assistant professor on TSRI’s Florida campus, has been awarded a $100,000 Alzheimer’s Association international grant to study the mechanisms of a pair of molecules involved in the progression of Alzheimer’s disease. The new two-year study will focus on the role of the regulating protein known as Rheb, which many believe may be active in neural plasticity, and its relationship with another molecule known as BACE1, an important enzyme in Alzheimer’s disease.

Joanne Doherty Receives Florida Center for Tumor Brain Research Grant

Joanne Doherty, senior staff scientist in the Guo lab, has received a grant from the Florida Center for Brain Tumor Research, in partnership with Accelerate Brain Cancer Cure, supporting work on the cutting edge of scientific inquiry, including development of innovative gene, virus, nanoparticle and immunity-based therapies, according to the award announcement.

Doherty’s research focuses on interfering with protein synthesis machinery specifically to kill glioblastoma tumor cells.
Leading Philanthropists Attend Conference on Scripps California Campus

TSRI recently hosted two full days of lectures and activities as part of a conference that drew philanthropists and special guests to San Diego from around the world.

The Cavendish Health Impact Forum featured speakers including philanthropists and community leaders Malin Burnham, Irwin Jacobs, Bob Klein and Denny Sanford, TSRI Acting President and CEO Jim Paulson, TSRI faculty members including Professor of Genomics Eric Topol, and scientists and executives from other San Diego research institutions.

“We were honored to host the Cavendish Foundation families for two days of the Cavendish Forum,” said Paulson. “It was a wonderful opportunity to network with the participants and introduce to them the entrepreneurial spirit of TSRI that underlies our history of turning basic discoveries into products that impact human health.”

Celebrating the Dorris Neuroscience Center

TSRI’s Dorris Neuroscience Center held its fifth annual Founder’s Day Celebration in May. Located on the La Jolla campus, the center is focused on understanding the human brain and nervous system and developing breakthrough treatments for neurological diseases.

Many of the center’s investigators conduct research within the Harold L. Dorris Neuroscience Center Building, a 53,000 square-foot-building with state-of-the-art facilities for imaging and behavioral studies, in their exploration of some of the most fundamental questions in neuroscience research. These questions include: How do sensory systems process information? How do we store and retrieve memories? What are the mechanisms involved in sensory impairment such as hearing loss or diseases such as schizophrenia, autism spectrum disorder, and depression? And what are promising new strategies to treat such diseases? Dorris Neuroscience Center researchers are leading the way forward.

Angling to Fight Cancer

A Scripps Florida scientist recently traded his lab equipment for fishing rods to take in some deep sea fishing off South Florida coastal waters. And although it may have looked as if he were in it purely for the fun, he was also angling to support the fight against cancer.

Scripps Florida Associate Professor and cancer researcher Joe Kissil boarded the 41-foot fishing vessel “You’re Done” along with his father George and a half dozen other anglers in this year’s 20th Annual Grand Slam KDW fishing tournament. The event in part benefited the Rendina Family Foundation, which supports TSRI in the area of cancer research.

Although Joe’s 11.3 lb. dolphin didn’t reel in a top prize for the tournament, Scripps Florida was well represented among the nearly 200 boats participating in the day-long event. The researcher’s participation also helped raise awareness among the other anglers of TSRI’s presence in the community and its ongoing research in fighting cancer.
NEW YORK TIMES best-selling author Tess Gerritsen is launching her second crowdsourced “War on Alzheimer’s” campaign to raise funds for Alzheimer’s research at The Scripps Research Institute (TSRI). Gerritsen is calling for fans, readers, and fellow authors to raise more than $50,000 through online donations on the crowdsourcing site GoFundMe.com.

“Watching my father lose his identity as he struggled with Alzheimer’s is the most devastating experience our family has been through,” said Gerritsen, whose work inspired the popular television series Rizzoli & Isles. “This campaign allows us to support the heroic scientists battling this terrifying disease and brings us closer to finding a cure. I truly believe we are almost there.”

The 2013 “War on Alzheimer’s” campaign raised over $50,000 in donations using incentives such as the chance to win naming rights in Gerritsen’s novel “Die Again,” published in December 2014. Gerritsen is again offering a few lucky fans who contribute to this year’s campaign the chance to name characters in her next Rizzoli & Isles novel, set for release in 2016.

Once again, Gerritsen has pledged to match $25,000 to encourage participation and beat the previous campaign total of $50,000.

For more information or to contribute to the campaign, visit GoFundMe.com/WOA-2015

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

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