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RESEARCH UPDATES

Findings Point to New Therapy Against Prostate and Other Cancers

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have found that a drug candidate with anticancer potential can be activated by one of the body’s natural responses to cellular stress. Once activated, the agent can kill prostate cancer cells.

“There is no proven drug right now with these activities,” said Ben Shen, vice chair of TSRI’s Department of Chemistry and senior author of the new study, “so this points the way toward a new therapeutic opportunity.”

The study, published by the journal *Proceedings of the National Academy of Sciences*, highlights the potential of the natural compound called leinamycin E1 (LNM) for development as a “prodrug,” a medication converted through a metabolic process in the body to become an active therapy.

Shen’s research has focused on developing natural products into potential therapies. As part of this effort, he heads the Natural Products Initiative at TSRI, a library with more than 3,000 strains and 450 pure natural products available for screening.

Chemists Find Efficient, Scalable Way to Synthesize Potential Brain-Protecting Compound

TSRI chemists have invented the first practical, scalable method for synthesizing jiadifenolide, a plant-derived molecule that may have powerful brain-protecting properties.

Finding a good way to synthesize jiadifenolide has been a goal of chemists around the world since the compound was discovered in 2009. Preliminary studies hinted it might be useful in protecting brain cells from neurobiological conditions such as Alzheimer’s, stroke and traumatic brain injury. But it is very difficult to obtain useful quantities of jiadifenolide from plants, and the synthesis methods reported in the past few years have low yields.

“Prior synthetic routes to jiadifenolide yield a few milligrams, suitable mainly for cell-culture experiments, but with our new method someone could make the gram to kilogram quantities needed for tests in animals and humans,” said Ryan A. Shenvi, associate professor at TSRI.

The feat by Shenvi and his team, described in a recent issue of *Nature Chemistry*, paves the way for the development of a jiadifenolide-derived drug.
Scientists Identify a Potential New Treatment for Osteoporosis

Scripps Florida scientists have identified a new therapeutic approach that, while still preliminary, could promote the development of new bone-forming cells in patients suffering from bone loss.

The study, published in the journal *Nature Communications*, focused on a protein called PPARy (known as the master regulator of fat) and its impact on the fate of stem cells derived from bone marrow (“mesenchymal stem cells”). Since these mesenchymal stem cells can develop into several different cell types—including fat, connective tissues, bone and cartilage—they have a number of potentially important therapeutic applications.

The scientists knew that a partial loss of PPARy in a genetically modified mouse model led to increased bone formation. To see if they could mimic that effect using a drug candidate, the researchers combined a variety of structural biology approaches to rationally design a new compound that could repress the biological activity of PPARy.

The results showed that when human mesenchymal stem cells were treated with the new compound, which they called SR2595 (SR=Scripps Research), there was an increase in osteoblast formation, a cell type known to form bone.

“These findings demonstrate for the first time a new therapeutic application for drugs targeting PPARy, which has been the focus of efforts to develop insulin sensitizers to treat type 2 diabetes,” said Patrick Griffin, chair of the Department of Molecular Therapeutics at Scripps Florida.

Small RNAs Found to Play Important Roles in Memory Formation

Scripps Florida scientists have found that a type of genetic material called “microRNA” plays surprisingly different roles in the formation of memory in animal models. In some cases, these RNAs increase memory, while others decrease it.

“Our systematic screen offers an important first step toward the comprehensive identification of all miRNAs and their potential targets that serve in gene networks important for normal learning and memory,” said Ron Davis, chair of TSRI’s Department of Neuroscience who led the study. “This is a valuable resource for future studies.”

The study was published in the June 2015 edition of the journal *Genetics*.

Unlike some types of RNA, microRNAs (miRNAs) do not code for proteins but instead regulate various biological processes by modulating the level of gene expression. A number of studies have shown that miRNAs are critical for normal development and cellular growth and may contribute to the complexity of neurodegenerative diseases.

In the new study, 134 different miRNAs were tested for roles in learning and memory in the central nervous system of *Drosophila melanogaster*, the common fruit fly, which is a recognized animal model for memory studies.

AIDS Vaccine Candidate Successfully ‘Primes’ Immune System

New research led by scientists at TSRI, the International AIDS Vaccine Initiative (IAVI) and The Rockefeller University shows in mice that an experimental vaccine candidate designed at TSRI can stimulate the immune system activity necessary to stop HIV infection. The findings could provide key information for the development of an effective AIDS vaccine.

The research, published in concurrent studies in the journals *Cell* and *Science*, represents a leap forward in the effort to develop a vaccine against HIV, which has so far struggled to elicit antibodies (immune system molecules) that can effectively fight off different strains of the virus.

“The results are pretty spectacular,” said Dennis Burton, chair of the TSRI Department of Immunology and Microbial Science and scientific director of two centers at TSRI, the IAVI Neutralizing Antibody Consortium (NAC) and the National Institutes of Health (NIH) Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID).

The *Science* study was co-led by Burton, TSRI Professor and IAVI NAC Director of Vaccine Design William Schief, and TSRI Professor David Nemazee. The *Cell* study was co-led by Schief and Michel Nussenzweig, who is Zanvil A. Cohn and Ralph M. Steinman Professor at The Rockefeller University and a Howard Hughes Medical Institute investigator.

Drug Candidate Significantly Reduces HIV Reactivation Rate

HIV-infected patients remain on antiretroviral therapy for life because the virus survives over the long-term in infected dormant cells. Interruption of current types of antiretroviral therapy results in a rebound of the virus and clinical progression to AIDS.

The study was published in the June 2015 edition of the journal *Genetics*. 
But now, scientists from Scripps Florida have shown that, unlike other antiretroviral therapies, a natural compound called Cortistatin A reduces residual levels of virus from these infected dormant cells, establishing a near-permanent state of latency and greatly diminishing the virus’ capacity for reactivation.

“Our results highlight an alternative approach to current anti-HIV strategies,” said Susana Valente, a TSRI associate professor who led the study. “Prior treatment with Cortistatin A significantly inhibits and delays viral rebound in the absence of any drug. Our results suggest current antiretroviral regimens could be supplemented with a Tat inhibitor such as Cortistatin A to achieve a functional HIV-1 cure, reducing levels of the virus and preventing reactivation from latent reservoirs.”

Modern Alchemy: Chemists Devise Synthesis of Valuable Exotic Compounds

TSRI chemists have discovered a broad and strikingly inexpensive method for synthesizing “amines,” a class of organic compounds prominent in drugs and other modern products. The new reaction is particularly useful for synthesizing complex amines that would be highly valuable in pharmaceuticals, but are impractical—or impossible—to make with standard methods. Yet the reaction requires little more than the mixing of two abundant compounds, a nitroarene and an olefin, with an iron catalyst.

“This is interesting science because a transformation like this has never been seen before,” said Phil S. Baran, the Darlene Shiley Chair in Chemistry at TSRI who led the new study. “Part of what’s unique about this scientific advance is that it’s also being immediately applied by industry—it’s just pretty darn useful. It’s as if we’re taking dirt, and then adding a bit of rust, and putting it all in a blender and ending up with gold—except that the amines we can make with this new method are often worth much more than their weight in gold.”

The findings were reported in a recent issue of the journal Science.

Scientists Pinpoint Mechanism for Altered Brain Growth in Autism Spectrum Disorder

As early as 1943, when autism was first described by psychiatrist Leo Kanner, reports were made that some, but not all, children with autism spectrum disorder have relatively enlarged heads. But even today, more than half a century later, the exact cause of this early abnormal growth of the head and brain has remained unclear.

Now, scientists from Scripps Florida have uncovered how mutations in a specific autism risk gene alter the basic trajectory of early brain development in animal models.

The study, published recently in The Journal of Neuroscience, focused on the gene PTEN (Phosphatase and tensin homolog), which is mutated in around 20 percent of individuals with autism spectrum disorder and enlarged heads (macrocephaly).

In new research, the team led by Scripps Florida biologist Damon Page found that mutations in the mouse version of PTEN, which approximate those found in a subgroup of individuals with autism spectrum disorder, lead to dynamic changes in the number of two key cell types that make up the brain—neurons and glia. At birth, neurons are more abundant than normal. Surprisingly, in adulthood the number of neurons in the brains of mutant animals is virtually the same as normal, and glia (which provide support for neurons) are overrepresented.

Scripps Florida scientists have uncovered how mutations in a specific autism risk gene alter the basic trajectory of early brain development.
The Scripps Research Institute (TSRI) has received a $12.5 million challenge grant from an anonymous donor to anchor the construction funding for a new building complex on the institute’s La Jolla campus.

The gift to TSRI is contingent on raising an additional $12.5 million in matching gifts for the project by the first quarter of 2018.

“I am extremely pleased to announce this generous and inspiring pledge,” said TSRI Acting President and CEO Jim Paulson. “The gift and matching funds will support TSRI’s world-renowned research by providing additional advanced laboratories and new operating efficiencies.”

“Thanks to this generous donor, every contribution to this important project will be amplified,” said Dick Gephardt, Chair of the TSRI Board and President/CEO of Gephardt Government Affairs. “The challenge grant is a meaningful invitation to other members of the community to join us in an initiative key to Scripps’s work expanding the frontiers of knowledge and finding new ways to combat disease.”

Paulson added the planned facilities will consolidate research labs on the La Jolla campus, encourage collaboration among the institute’s scientists and strengthen ongoing programs in global health, neuroscience, addiction, structural biology and immunology.

The building complex, projected to open in 2019, will include two laboratory buildings totaling 147,000 square feet of space and an advanced 12,000-square-foot nuclear magnetic resonance (NMR) facility. These buildings will be highly energy efficient, meeting Leadership in Energy & Environmental Design (LEED) green building standards.
Situated at the intersection of John Jay Hopkins Dr. and Genesee Avenue, the new complex is planned on a site adjacent to TSRI’s electron microscopy suite, graduate offices and architecturally renowned auditorium and plaza. Currently, the site is occupied primarily by a parking lot, which will be replaced by a four-level parking structure and subterranean parking spaces under the laboratory buildings.

The total cost for design and construction of the project is estimated at $111 million, which will also involve long-term financing.

Over the long-term, the new facilities will reduce the institute’s operating costs. Once the complex is complete, total savings are projected at approximately $12 million per year in leases, utilities and other expenses.

To give to TSRI’s building campaign or to learn more, please contact Director of Philanthropy Christopher Lee, (858) 784-2037, clee@scripps.edu.

The new complex is projected to open in 2019.

Facts at a Glance

BUILDINGS
The planned facilities on the Scripps California campus will provide:

- Two two-story state-of-the-art laboratory buildings with 147,000 square feet of space for advanced biomedical research
- An updated 12,000-square-foot nuclear magnetic resonance (NMR) facility
- A four-level parking structure with a capacity of 658 vehicles (in addition to subterranean parking under the laboratory buildings)
- Construction to green building certification standards set by the Leadership in Energy & Environmental Design (LEED)

ADVANTAGES
- Providing state-of-the-art laboratories for TSRI’s biomedical research, which advances innovative treatments for conditions from Alzheimer’s to stroke
- Saving an estimated total of $12 million per year on facilities-related expenses such as leases and utilities

CONSTRUCTION TIMETABLE
- Completed: Initial development plans drawn and permits submitted
- 2015: Detailed architectural and construction planning
- 2016 Q2: NMR facility construction begins
- 2017 Q2: Parking structure construction begins
- 2018 Q1: Laboratory building construction begins
- 2019 Q2: All facilities complete
Tell us about your research and the diseases it impacts.
I conduct basic (discovery) research in immunology. The immune system is critical to human health, but it’s a tricky thing. The immune system needs to discriminate between what is normally part of our body (“self”) and what should not be there (“non-self”)—bacteria and viruses, for example. Receptors on antibody-forming B lymphocytes and T lymphocytes enable the immune system to respond to foreign pathogens without harming one’s own tissues. A failure in this system can result in autoimmune disease such as type 1 diabetes, where the immune system attacks cells in the pancreas that produce insulin.

In particular, our lab has been examining how expression of proteins in normal tissues or tumor cells alters recognition and responsiveness by T lymphocytes to antigens (immune-stimulating components). The problem with cancer is the immune system identifies it as “self” and prevents immune attack. We have tweaked, prodded and pushed immune cells into successfully attacking tumors and enhancing the body’s ability to fight cancer. These new tools basically get the immune system to pay attention to cancer cells and go after them. We believe our work in mice provides a foundation for effective, non-toxic immunotherapy for cancer patients.

What are you trying to accomplish and what motivates you most about your work?
It’s important to me to determine how to promote the destruction of cancer by the immune system. New discoveries get me excited. The best part of my day is talking with my lab colleagues about their scientific data and then analyzing this data to make new discoveries to combat disease.

How can philanthropy help your research?
We have a particular need for funds to develop our work in tumor immunotherapy. Tumor immunotherapy offers the most promising and powerful potential for patients with late-stage lung and bladder cancer and melanoma, with an unheard of 40 to 60 percent response rate. It was the hottest topic at the most recent American Association for Cancer Research annual meeting. In addition to our lab, others at TSRI are doing work in this area, and it would be great to have a consolidated program – it’s very exciting to think about.

What do you like about TSRI?
I love my extraordinary colleagues and our very supportive environment. We can spend so much time doing research here, unfettered by the mundane bureaucratic activities at a traditional university. It’s the philosophy that Frank Dixon and the “Pitt Five” brought to TSRI when they came here from the University of Pittsburgh in 1961 to initiate TSRI’s modern era – an institute set up for scientists to perform their research and achieve their goals without worry about bureaucratic details.
What is the new Female Faculty Group at TSRI and why did you choose to get involved?

The group, consisting of about 50 female faculty members, came together last summer with a mission to share the significance and value of TSRI research. We’re proud of our accomplishments at TSRI and enthusiastic about telling the public about our science. Plus, the Female Faculty Group brings us together across the many buildings and departments on our campuses in La Jolla and Jupiter.

At our first Female Faculty event in February, about 80 community members and TSRI faculty shared wine, snacks and the latest breakthroughs in biomedical research by some of our female scientists. In addition to reaching out to community members, the group has started collaborating more in their own research projects. It has been very fruitful.

Tell us about what you hope to accomplish as a TSRI Trustee.

I’m excited to have recently been elected, along with Patrick Griffin from our Florida campus, as one of the first faculty members to join the TSRI Board of Trustees. Many academic institutions have faculty on their boards and I’m glad we are joining their ranks.

I feel that the addition of faculty members to the board represents a significant step in the evolution of TSRI’s governance – it makes the trustees more cognizant of what goes on in the day-to-day lives of our faculty and will impact important decisions. It also augments my role as chair of the Faculty Council of TSRI, which is a reinvigorated group of faculty members across departments who advise the institute’s president on various issues.

Tell us about your current role as president of the American Association of Immunologists (AAI).

I’ve been president the past year and it’s near and dear to my heart. The AAI is a longstanding international organization of scientists, with more than 7,000 members, dedicated to advancing knowledge of immunology. I’ve been an active member of AAI for more than 30 years and on the Council for the past six.

We’ve spearheaded many programs to help fund young scientists in a tough funding environment, through fellowships, travel to other labs and regional awards. Most importantly, we lobby Congress and I spend time on Capitol Hill each year discussing the importance of funding basic science both in terms of the financial benefits to communities and the health benefits of discovering cures for diseases.

Mark your calendars for an event on the Scripps California campus featuring Dr. Sherman on Wednesday, October 21. See www.scripps.edu/california/philanthropy/events.html
Researcher Wins $4.5 Million in Gates Foundation Grants to Support Development of AIDS Vaccine

A group at TSRI led by Associate Professor Andrew Ward has been awarded two grants from the Bill & Melinda Gates Foundation totaling more than $4.5 million to fund efforts to develop a vaccine against HIV/AIDS.

“We are delighted by the Gates Foundation’s support of this critical work,” said Jim Paulson, acting president and CEO of TSRI. “With 35 million infected individuals worldwide, an effective HIV vaccine is urgently needed to slow and ultimately eliminate new infections.”

The new grants, awarded through the foundation’s Collaboration for AIDS Vaccine Discovery (CAVD) program, will provide new tools in TSRI’s High Resolution Electron Microscopy Facility to collect and process high-resolution images of HIV proteins interacting with antibodies (immune molecules), giving scientists a picture of which immunogens (substances that induce immunity) are most effective and why.

Scientists Win $2.1 Million to Study Protein Linked to Parkinson’s Disease

Scripps Florida scientists have been awarded $2.1 million from the National Institute of Neurological Disorders and Stroke of The National Institutes of Health (NIH) to study a protein that has been closely linked in animal models to Parkinson’s disease and Huntington’s disease.

TSRI Assistant Professor Srinivasa Subramaniam will be the principal investigator of the new five-year grant.

The focus of the new study is a multifunctional protein known as rapamycin (mTOR), which is involved in embryonic development, cancer and diabetes. Malfunction in mTOR activity—either too much or too little—has also been linked to a variety of brain dysfunctions such as epilepsy, mental retardation, Huntington’s disease and Parkinson’s disease.

$1.5 Million Grant Funds Study New Strategies for Parkinson’s Disease and Other Disorders

Scripps Florida scientists led by Associate Professor Douglas Kojetin have been awarded nearly $1.5 million from the National Institute of General Medical Sciences of the NIH to explore the therapeutic potential of a class of proteins that play essential roles in the regulation and maintenance of human health.

These proteins are expressed throughout the body, including the central nervous system during brain development, and are associated with conditions including Parkinson’s disease, inflammation, arthritis, cancer, metabolic disorders (dyslipidemia, obesity, diabetes) and cardiovascular disease.
Joseph Schonhoft Named Damon Runyon Fellow

Joseph Schonhoft, research associate in the Kelly lab, is one of just 16 newly named Damon Runyon Fellows nationwide. The four-year award supports outstanding postdoctoral scientists conducting basic and translational cancer research in the laboratories of leading senior investigators.

In his current project, Schonhoft aims to understand how immune cells abnormally proliferate and secrete antibody proteins that cause organ and tissue damage during diseases such as amyloidosis and certain multiple myelomas, information that could be used to develop new diagnostic probes to improve the effectiveness of current clinical treatments.
Matthew Disney, a professor on TSRI’s Florida campus, and Leonard Petrucelli, chairman of the Department of Neuroscience for the Mayo Clinic in Jacksonville, have been awarded $500,000 by the ALS Association from proceeds from last summer’s Ice Bucket Challenge.

The grant will support work on pre-clinical evaluations of potential drug candidates, specifically small molecules that target a mutation in the C9orf72 gene that causes the common genetic form of amyotrophic lateral sclerosis (ALS).

ALS, the disease that killed well-known baseball player Lou Gehrig, is a progressive neurodegenerative disease that destroys motor neuron cells that control muscle movement. More than 30,000 Americans have ALS and nearly 6,000 are diagnosed with the devastating disease each year.

To support research at TSRI on ALS and other diseases, go to www.scripps.edu/support.

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