Research Update

Researchers Develop Test to Predict Early Onset of Heart Attacks

A new “fluid biopsy” technique that could identify patients at high risk of a heart attack by identifying specific cells as markers in the bloodstream has been developed by a group of researchers at The Scripps Research Institute (TSRI).

The technique works by identifying circulating endothelial cells (CECs) and has been successful in distinguishing patients undergoing treatment for a recent heart attack with a healthy control group.

The researchers believe the technique can now be tested on patients who exhibit symptoms but are yet to experience a heart attack. Currently, there is no predictive test for a heart attack—at least not of satisfying accuracy.

“The goal of this paper was to establish evidence that these circulating endothelial cells can be detected reliably in patients following a heart attack and do not exist in healthy controls—which we have achieved,” said TSRI Associate Professor Peter Kuhn, who led the study. “Our results were so significant relative to the healthy controls that the obvious next step is to assess the usefulness of the test in identifying patients during the early stages of a heart attack.”

Scripps Florida Scientists Find Regulator of Amyloid Plaque Buildup in Alzheimer’s Disease

Scientists from the Florida campus of The Scripps Research Institute have identified a critical regulator of a molecule deeply involved in the progression of Alzheimer’s disease.

The new study, published in the *Journal of Biological Chemistry*, shows for the first time that levels of this regulating protein are decreased in the brains of Alzheimer’s disease sufferers and that this decrease could be a significant factor in the advance of the disease.

The regulator is known as Rheb, a protein that many believe may be active in neural plasticity, the ability of the brain to change in response to learning.

In the new study, the scientists found that Rheb binds and regulates activity of a molecule known as BACE1, an important enzyme in Alzheimer’s disease pathology, establishing for the first time a new molecular link between Rheb and BACE1.

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Is Your Will a “Won’t?”

> If your will is valid and up-to-date, pat yourself on the back. You have done what many fail to do. You thought about important matters and made decisions. You went to an attorney and put those thoughts on paper. Then, you signed it.

But there are many of us who fail to plan (or plan to fail?). We put off important decisions and talking with a qualified attorney. Our will is just a “won’t,” and instead of claiming, “Did it,” we can only say, “Didn’t.”

Take a look at the following 10 reasons for not having a will. Mark the box if any apply to you.

- I don’t have time to work on my will.
- I don’t have an attorney who can draft my will.
- I cannot afford to pay for a will right now.
- My estate is too small to bother with a will.
- I can’t deal with the idea of dying.
- I worry that my decisions might cause family disagreements.
- I can’t get to the attorney’s office.
- I’m too young for a will; I’ll get one when I’m older.
- I don’t know who to name as executor (or guardian, etc.).
- I’ll just let my survivors make all the decisions.

Now, were any of these items marked by you? If so, perhaps consider visiting our website and using our Will Planning Wizard or allow us to send you a hard copy version. The Will Planning Wizard begins the will preparation process. It does not create a will or a legal document. Instead, it guides you in collecting and organizing your thoughts, information, and documents before you visit your attorney. Beyond that, our planned giving staff can help direct you to find a good attorney and handle everything in confidence.

You can start by visiting our website at www.plannedgiving.scripps.edu and clicking on the Will Planning Wizard page or simply contact Geoff Graham, director, planned giving and estates, at (858) 784-9365 or gegraham@scripps.edu. In Florida, contact Irv Geffen, director of major gifts and planned giving, 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.
Scripps Florida Scientists Identify Potential New Drug for Inherited Cancer

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have identified a new drug candidate for an inherited form of cancer with no known cure.

The new study showed the drug candidate—known as FRAX97—slowed the proliferation and progression of tumor cells in animal models of Neurofibromatosis type 2. This inherited type of cancer, caused by mutations in the anti-tumor gene NF2, leads to tumors of the auditory nerve that connects the inner ear to the brain.

The new compound, originally developed to treat neurodegenerative disease, 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 Neurofibromatosis type 2. PAK1 has also been implicated in the growth of breast and lung cancers.

“Our study shows that if we inhibit these kinases we can counter the formation of tumors in this brain disease,” said Joseph Kissil, a TSRI associate professor who led the study.

In the new study, published in *The Journal of Biological Chemistry*, Kissil and his colleagues showed that the inhibitor slows down progression of Neurofibromatosis type 2 in animal models and reduces more than 80 percent of PAK1 activity.

Kissil notes a key challenge in developing drug candidates is finding potential agents that are both potent and highly selective for their targets—limiting its action to the desired arena and reducing unwanted side effects.

“This inhibitor turned out to be both potent and highly selective,” he said. “The real question is why. We were able to show that it works through a unique mechanism.”

While the binding site on PAK1 is quite large, it also contains a smaller pocket, a kind of backroom that juts off the larger site. The inhibitor not only takes up space in the larger site, but enters the back pocket as well. That extra binding gives the inhibitor its strong selectivity.

New Map of Insulin Pathway Could Lead to Better Diabetes Drugs

A team led by scientists at The Scripps Research Institute (TSRI) has created the first comprehensive roadmap of the protein interactions that enable cells in the pancreas to produce, store and secrete the hormone insulin. The finding makes possible a deeper scientific understanding of the insulin secretion process—and how it fails in insulin disorders such as type 2 diabetes.

“The development of this insulin interaction map is unprecedented, and we expect it to lead us to new therapeutic approaches for type 2 diabetes,” said William E. Balch, professor and member of the Skaggs Institute for Chemical Biology at TSRI.

Balch was the senior author of the study, which was recently reported in the journal *Cell Reports*. 
DONOR PROFILE

Middle School Student Raises Funds for Alzheimer’s Research at TSRI

Twelve year old Jenny Kafas doesn’t know anyone with Alzheimer’s, but after watching a film about a woman with the disease, she was moved to tears and knew she wanted to help. The determined middle school student spent last summer, when she was eleven, utilizing her creative talents by making and selling purple lanyard keychains, raising $128 for Alzheimer’s research at The Scripps Research Institute (TSRI).

A seventh grade student at Franklin Middle School in Somerset, New Jersey, Jenny was deeply touched while watching the movie The Notebook. The film tells the story of a couple who in their later years find themselves affected by Alzheimer’s disease.

“I was upset that the woman, who had been married to her husband for years, was dancing with him and could not remember who he was or who her children and grandchildren were,” said Jenny. After seeing this, I wanted to make a difference.”

While many of her peers were playing games, going on vacation, or going to theme parks, Jenny spent the summer raising money for Alzheimer’s research. She decided to make TSRI the beneficiary for her fundraising after finding the institute online and being impressed with its high rating for accountability and transparency. “I wanted most of what I raised to go into actual research,” said Jenny.

Jenny did further research and found that purple is the “color” of Alzheimer’s disease. Since she enjoys making lanyards anyway, she decided to create purple lace Alzheimer’s awareness ribbon lanyards to raise funds. She started the project in August. The campaign went so well it stretched into September.

“I asked for a $3 contribution from family, friends, and neighbors,” said Jenny. “But a lot of people gave even more, and my godparents bought many to give as gifts. I didn’t realize how many people had family members or friends with Alzheimer’s—I received a really touching note that impacted me from one of my contributors on how important this was as her mother had suffered from Alzheimer’s.”

“I had hoped to raise maybe $30 initially, not $128—it went way beyond what I’d thought!” Jenny continued. “I was really pleased with the response and how much we raised for Alzheimer’s research. It was a fun way to do something positive to help—even if you don’t have anyone in your family now with the disease, it could still happen and we need a cure. I’m just a normal kid, and I think the campaign showed that children can make a big difference to society if they choose to.”

“Jenny wanted to do everything she could to help,” said her mother, Suzanne. “My husband Demetris and I are so proud of her. She worked hard and felt very strongly about this. I can’t say we’re entirely surprised—she is always looking for ways to help on issues and problems.”

“We are so impressed by Jenny’s determination to help raise money for our pioneering research,” said William Burfitt, director of philanthropy at TSRI. “We can’t thank her enough for her fantastic efforts.”

Asked about a possible future in fundraising, Jenny replied that she may be looking to raise some more funds next summer with the help of some friends—a born fundraiser!

“We found that Rheb regulates BACE1, which is a major drug target in Alzheimer’s disease,” said Srini Subramaniam, a TSRI biologist who led the study. “Studies of the autopsied brains of Alzheimer’s patients have found a significant reduction in Rheb, so it is possible that an increase in Rheb could reverse the buildup of amyloid plaque.”

The study noted that in some genetically modified animal models, an increase of Rheb has already been shown to reduce BACE1 levels and the production of amyloid plaque.

“If we can uncover the mechanism by which Rheb alters BACE1 levels, that would be a very good drug target,” said Neelam Shahani, a first author of the study with William Pryor, both research associates in the Subramaniam lab.
Tell us about your research and the diseases it impacts.

I develop technologies that detect disease, as well as treatments for diseases. Our lab has broad interests—including neglected tropical diseases, emerging drugs of abuse, and melanoma.

Our work on emerging drugs of abuse is focused on understanding why people become addicted, so we can prevent it and to develop vaccines to assist people who want to quit. Four years ago, my colleague, TSRI Associate Professor Michael Taffe, and I, noticed a sudden rise in press reports from the U.K. on the dangerous effects of “bath salts” on users there; we knew it was just a matter of time before these emerging recreational drugs reached the U.S. We recently published one of the first laboratory studies of bath salts, which confirmed the drug’s powerful stimulant effect in rats and found evidence that it could be more addictive than methamphetamine, one of the most addictive substances known to date. High doses of bath salts bring a strong risk of paranoid psychoses, violence and suicide.

I’m also proud of our work in chronic and debilitating parasitic diseases that affect hundreds of millions of people worldwide. I was involved in the development of the first screening method to rapidly identify individuals with active river blindness, a parasitic disease that afflicts and causes misery for an estimated 37 million people. The test could change the current strategy of mass treatment in areas where river blindness is suspected. The vast majority of river blindness infections occur in sub-Saharan Africa, with the largest disease burden in rural Nigeria. Humans acquire the disease after they are repeatedly bitten by black flies that harbor a type of worm that breeds near fast moving rivers.

It’s not often that you get to present your work to a former president of the United States. President Carter met with us and took a keen interest in our work on developing diagnostic tools for parasitic diseases, underlining the huge impact it could have in developing countries. The meeting was a tremendous energizer. I met President Carter a second time at a meeting in Coronado. I was gratified that he remembered me, and he again declared his support for our work. It was a big boost to know he cared.

Finally, we’re currently developing a diagnostic platform for melanoma and will hopefully have a treatment in clinical trials in the next twelve months. The survival rate for melanoma is extremely low at five percent—we’re in need of diagnostics that detect the disease early.

What motivates you?

When I was younger, I just loved being in the lab. Now that I’m older and married with three children, I’m excited about how we can use science to impact people’s lives. I traveled to Nigeria in 2009, and saw the impact of parasitic diseases first-hand. It made my work far less esoteric. I want to go beyond basic science to see my work contribute to the good of humankind.

Has philanthropy been useful to your work? Why is it important?

The impetus for helping in the fight to eradicate river blindness came from entrepreneur and philanthropist John Moores—who has helped fund our work. John conveyed his passion for fighting this disease. Now we have a tool that helps us meet one of the major challenges of medicine for this century—true elimination and eradication of infectious disease. Not just treatment, but true eradication. Philanthropy will need to play a bigger role on our work in tropical diseases moving forward—it is research that is not typically funded by the federal government, and philanthropists tend to be more nimble in responding to emerging needs. In the next twenty years, donors will make a really big difference in what types of science and medical research will take place—donors shape where discoveries are made.

What brought you to TSRI and what do you like about it?

I came here as a graduate student in 2000 and have been here ever since. The reason I came was the combination of basic chemical science with access to biology, and I liked the faculty. The level of science is what keeps me here. The access to colleagues and technology is truly unique.
Jim Graziano: Developing Innovative Drugs Using a Next Generation Approach

A fter receiving his doctorate from TSRI’s graduate program in 2005, Jim Graziano has gone on to great things. He is currently Chief Operating Officer of Fabrus, Inc., a La Jolla, California firm with a next generation approach to delivering drug candidates, where he is responsible for day-to-day operations.

Originally from San Jose, after graduating from high school, Jim spent some time as an industrial plant mechanic and a nuclear propulsion plant mechanic in the U.S. Navy, before receiving his BA from the University of California, Berkeley.

He was at TSRI as a graduate student from 1999 to 2005, where his advisor was Peter Schultz, a revered scientist who serves as Professor of Chemistry at TSRI.

“The TSRI graduate program was wonderful—the class sizes were small and I made a number of good friends who I’m still in touch with,” said Jim. “I liked the environment—it was much more collaborative than I would have encountered in a traditional university, which tend to be more top-down. Plus, there was a strong entrepreneurial emphasis, which you don’t find in typical academia—the TSRI graduate program is structured well for students who want to excel in industry. It also helped me develop a great network. The most important thing I learned in grad school, besides being a good scientist, is the value of networking.”

After leaving TSRI, Jim undertook a short postgraduate fellowship at the Genomics Institute of the Novartis Research Foundation (GNF), and then served as a Staff Scientist at Kythera Biopharmaceuticals, Inc. for a year, where he was involved in the development of dermatological drugs.

Jim joined Fabrus, Pfizer’s first incubator company in 2007. The goal of the Pfizer Incubator was to capture the innovation of freewheeling, early-stage biotechs, providing them with resources, without smothering them, and to help bring innovative technologies and drug candidates into Pfizer’s R&D pipeline. Fabrus, founded by TSRI Assistant Professor Vaughn Smider, went independent two years later.

“Our vision is to dramatically expand the clinical impact of antibodies,” said Jim. “Current methods of antibody discovery have failed to identify therapeutic candidates to difficult membrane-bound targets. We have revolutionary next generation approaches, involving high throughput antibody screening automation and a new antibody scaffold discovered in Dr. Smider’s TSRI lab, to discover and develop new antibody drug candidates. We’re committed to developing highly innovative treatments to impact multiple diseases, and are making strides, notably in developing novel drug candidates for cancer—we’re hoping to have two drugs ready for the clinic within a couple years.”

“We’ve done a lot with very few resources to now, but with recent financial backing from Opko Health, we’re enthusiastic about the future, and are poised to make leaps and bounds,” said Jim.

At Fabrus, Jim is able to utilize his extensive experience in protein engineering, and the management and implementation of lab automation, such as laboratory robotics. Fabrus employs eight scientists.

“I’m responsible for the day to day operations and wear lots of hats,” said Jim. “I love what I do, and I’m always learning—the job combines my technical and mechanical background with my supervisory skills—I feel like I’m helping to guide where we’re headed, which hopefully will ultimately result in a new drug for treating cancer.”

Jim participated in the TSRI graduate program’s inaugural alumni symposium in 2012, serving on a career panel, where he spoke of his career activities since graduation, and offered job-seeking guidance.

“I found this panel rewarding and I look forward to another opportunity,” said Jim. “I have really enjoyed my alumni interaction. I’ve also entertained tours of graduate students and postdoctoral fellows from TSRI, including students from Scripps Florida, so that they can experience what a small company operating outside of the academic environment looks like. I like to give back—I feel my graduate training at TSRI provided me with a lot of professional development—it’s easy for me to give my time back.”
AWARDS AND HONORS

Scripps Research Institute Chemist Chi-Huey Wong Wins Prestigious Wolf Prize

Chi-Huey Wong, professor of chemistry at The Scripps Research Institute (TSRI), has won the 2014 Wolf Prize in Chemistry for his pioneering contributions to the synthesis of compounds vitally important to biology and medicine.

Sometimes cited as the most prestigious award after the Nobel Prize, the Wolf Prize is presented to living scientists and artists for "achievements in the interest of mankind and friendly relations among peoples" by the Israel-based Wolf Foundation, established in 1976 by the late German-born inventor, diplomat and philanthropist Ricardo Wolf.

“This very special honor for Chi-Huey is richly deserved,” said Scripps Research President and CEO Michael A. Marletta. “His fundamental chemistry has had a significant impact on medicine and biology and I am delighted this recognition has come to him and even more delighted that he has remained a Scripps colleague.”

The announcement of Wong’s award cited his development of methods to synthesize complex carbohydrates, glycoproteins and related substances that had been impossible or unfeasible to be synthesized by other methods. His work is used by carbohydrate chemistry and biology researchers to halt progression of cancer and viral infections, and increase immunological functions in the body. The research has led to the development of vaccines, therapeutics and glycan microarrays for analysis of protein-carbohydrate interaction.

Wong, who also serves as president of Academia Sinica in Taiwan, was presented a certificate and a $100,000 award with other Wolf Prize honorees from Israeli President Shimon Peres and Education Minister Shai Piron in a special ceremony in January at the Knesset (Israel’s Parliament).

Wong is the fourth TSRI scientist to receive the Wolf Prize in Chemistry. Previous institute winners include K. Barry Sharpless, Nobel laureate and W.M. Keck Professor of Chemistry; Richard A. Lerner, Lita Annenberg Hazen Professor of Immunochemistry and Institute Professor; and Peter Schultz, the Scripps Family Chair Professor.

Intern Eric Chen Wins Google’s Grand Prize

Eric Chen, high school intern in the Wilson lab at The Scripps Research Institute (TSRI), has won the grand prize in the 2013 Google Science Fair for his project “The Taming of the Flu,” research to help discover a new anti-flu medicine effective against all influenza viruses.

“This is a fantastic achievement, and we are very proud of Eric,” said TSRI Professor Ian Wilson. “It was extremely impressive that Eric was able come to our lab as a high school student with lot of ideas of how to tackle influenza virus and then proceed to follow through on them in the lab.”

The 17-year-old Canyon Crest Academy senior, who began his research while an intern at the University of California, San Diego, bested 14 other science fair finalists selected from tens of thousands of entrants worldwide. Chen captured not only his age category, but also the top overall prize, which includes a $50,000 scholarship and a National Geographic Expedition trip to the Galapagos Archipelago. Canyon Crest Academy also received a $10,000 technology grant on his behalf. The science fair award ceremony was televised live via YouTube from Google’s headquarters in Mountain View, California.

Currently applying to colleges for the fall, Chen is considering a career either as a university professor, which would allow him to both teach and perform research, or as an entrepreneur.
TSRI-Nikon Partnership Allows Scientists to See More Clearly, Probe Deeper

Researchers at The Scripps Research Institute (TSRI) can now probe more deeply and clearly into the microscopic elements of cells with the recent opening of a new Nikon Center of Excellence on the California campus, featuring the latest in advanced molecular and atomic imaging technology.

The center is an academic-industry partnership between the institute and optics systems provider Nikon Instruments, Inc. “We are pleased about this exciting new partnership with Nikon,” said Ulrich Mueller, chair of the Department of Molecular and Cellular Neuroscience and director of the Dorris Neuroscience Center (DNC). “It will provide researchers at TSRI with rapid access to the most modern imaging technology currently available. As an added advantage, we will be able to develop technological solutions to imaging problems that can be transformative for the research community as a whole.”

According to Nikon officials, the partnership aims to lower the barriers for establishing a state-of-the-art microscopy facility and to enable a free exchange of ideas, methodologies and technologies between TSRI investigators and Nikon’s development teams.

A ribbon-cutting on Tuesday, November 12, officially launched the new center. Located in the Dorris Neuroscience Center, the center’s space has been refurbished to accommodate the prototype equipment, which requires walls painted matte-black to eliminate gloss reflection that could impact the instruments’ laser function.

The imaging facility includes a newly installed Nikon N-SIM microscopy system, which produces nearly two times the resolution as conventional optical microscopes and enables detailed visualization of minute intracellular structures and their interactive functions. Coming soon is the Nikon A1 MP multi-photon confocal microscope, which features a high-resolution galvanometer scanner.

The center also offers other TSRI-owned Nikon instruments, including an A1R laser-scanning confocal imaging system, capable of high-speed capture of high-quality images of cells and molecular events with enhanced sensitivity, and N-STORM, a super-resolution fluorescence microscope technology.

Andrew Ward Wins Ray Thomas Edwards Foundation Award

TSRI Assistant Professor Andrew Ward is the recipient of the 2013 Ray Thomas Edwards Foundation Career Development Award, recognizing promising early-career scientists performing biomedical research initiated in San Diego County.

The $150,000 award will support Ward’s HIV vaccine research, which utilizes various biophysical techniques to investigate how neutralizing antibodies recognize HIV.

The Ray Thomas Edwards Foundation awards this prize each year to a scientist from TSRI, the Salk Institute for Biological Studies or the University of California, San Diego, who is within the first three years of his or her first faculty assignment.

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