Scientists at The Scripps Research Institute (TSRI) have shed light on one of the major toxic mechanisms of Alzheimer’s disease. The discoveries could lead to a much better understanding of the Alzheimer’s process and how to prevent it.

The findings show that brain damage in Alzheimer’s disease is linked to the overactivation of an enzyme called AMPK. When the scientists blocked this enzyme in mouse models of the disease, neurons were protected from loss of synapses—neuron-to-neuron connection points—typical of the early phase of Alzheimer’s disease.

continued on page 2

Philanthropist John Moores Gives $2 Million to The Scripps Research Institute to Develop River Blindness Field Test

Philanthropist, businessman and community leader John Moores has given The Scripps Research Institute (TSRI) approximately $2 million to fund the development of a new field test for Onchocerciasis, or river blindness, a parasitic infection that affects tens of millions of people in Africa, Latin America and other tropical regions.

“We are grateful for John’s generosity and foresight,” said Michael A. Marletta, president and CEO of TSRI. “This gift has the potential to revolutionize treatment of a disease that causes widespread suffering in the developing world. We are fortunate to have John as a long-time supporter who recognizes the impact our science can have to improve human health.”

Moores, former chair of the TSRI Board of Trustees, has been a leader in the fight against worm-carried conditions. In 2005, he founded the Worm Institute of Research and Medicine (WIRM) at TSRI with a $4 million gift. Previously, Moores founded the River Blindness Foundation to distribute a treatment in developing countries, principally in sub-Saharan Africa; in 1997, the foundation was absorbed into The Carter Center of Atlanta, where Moores is trustee emeritus.

Moores’s new gift to TSRI follows the publication of breakthrough results from the laboratory of Professor Kim D. Janda, who is director of WIRM, Ely R. Callaway, Jr. Chair and member of the Skaggs Institute for Chemical Biology at TSRI. In the new study, the team identified a biomarker, detectable in patients’ urine, that is secreted by Onchocerca volvulus worms during an active infection.

continued on page 7

Inside:
3 . . . The Benefits of Donating Securities
4 . . . Donor Profile: Leta Lindley
5 . . . Scientist Profile: Ian Wilson

RESEARCH UPDATE

Scripps Research Institute Scientists Help Unravel a Central Mystery of Alzheimer’s Disease

Scientists at The Scripps Research Institute (TSRI) have shed light on one of the major toxic mechanisms of Alzheimer’s disease. The discoveries could lead to a much better understanding of the Alzheimer’s process and how to prevent it.

The findings show that brain damage in Alzheimer’s disease is linked to the overactivation of an enzyme called AMPK. When the scientists blocked this enzyme in mouse models of the disease, neurons were protected from loss of synapses—neuron-to-neuron connection points—typical of the early phase of Alzheimer’s disease.

continued on page 2
“These findings open up many new avenues of investigation, including the possibility of developing therapies that target the upstream mechanisms leading to AMPK overactivation in the brain,” said TSRI Professor Franck Polleux, of the Dorris Neuroscience Center, who led the new study.

Alzheimer’s disease, a fatal neurodegenerative disorder afflicting more than 25 million people worldwide, currently has no cure or even disease-delays therapy.

In addition to having implications for Alzheimer’s drug discovery, Polleux noted the findings suggest the need for further safety studies on an existing drug, metformin. Metformin, a popular treatment for Type 2 Diabetes, causes AMPK activation.

Researchers have known for years that people in the earliest stages of Alzheimer’s disease begin to lose synapses in certain memory-related brain areas. Small aggregates of the protein amyloid beta can cause this loss of synapses, but how they do so has been a mystery.

Until recently, Polleux’s laboratory has been focused not on Alzheimer’s research but on the normal development and growth of neurons. In 2011, he and his colleagues reported that AMPK overactivation by metformin, among other compounds, in animal models impaired the ability of neurons to grow output stalks, or axons.

Around the same time, separate research groups found clues that AMPK might also have a role in Alzheimer’s disease. One group reported that AMPK can be activated in neurons by amyloid beta, which in turn can cause a modification of the protein tau in a process known as phosphorylation. Tangles of tau with multiple phosphorylations (“hyperphosphorylated” tau) are known to accumulate in neurons in affected brain areas in Alzheimer’s. These results, published two years ago, reported abnormally high levels of activated AMPK in these tangle-ridden neurons.

Polleux decided to investigate further, to determine whether the reported interactions of AMPK with amyloid beta and tau can in fact cause the damage seen in the brains of Alzheimer’s patients. “Very little was known about the function of this AMPK pathway in neurons, and we happened to have all the tools needed to study it,” he said.

Georges Mairet-Coello, a postdoctoral research associate in the Polleux lab, performed most of the experiments for the new study. He began by confirming that amyloid beta, in the small-aggregate (“oligomer”) form that is toxic to synapses, does indeed strongly activate AMPK; amyloid beta oligomers stimulate certain neuronal receptors, which in turn causes an influx of calcium ions into the neurons. He found that this calcium influx triggers the activation of an enzyme called CAMKK2, which appears to be the main activator of AMPK in neurons.

The team then showed that this AMPK overactivation in neurons is the essential reason for amyloid beta’s synapse-harming effect. Normally, the addition of amyloid beta oligomers to a culture of neurons causes the swift disappearance of many of the neurons’ dendritic spines—the rootlike, synapse-bearing input stalks that receive signals from other neurons. With a variety of tests, the scientists showed that amyloid beta oligomers can’t cause this dendritic spine loss unless AMPK overactivation occurs—and indeed AMPK overactivation on its own can cause the spine loss.

For a key experiment the team used J20 mice, which are genetically engineered to overproduce mutant amyloid beta, and eventually develop an Alzheimer’s-like condition. “When J20 mice are only three months old, they already show a strong decrease in dendritic spine density, in a set of memory-related neurons that are also affected early in human Alzheimer’s,” Mairet-Coello said. “But when we blocked the activity of CAMKK2 or AMPK in these neurons, we completely prevented the spine loss.”

Next Mairet-Coello investigated the role of the tau protein. Ordinarily it serves as a structural element in neuronal axons, but in Alzheimer’s it somehow becomes hyperphosphorylated and drifts into other neuronal areas, including dendrites where its presence is associated with spine loss. Recent studies have shown that amyloid beta’s toxicity to dendritic spines depends largely on the presence...
of tau, but just how the two Alzheimer’s proteins interact has been unclear.

The team took a cue from a 2004 study of *Drosophila* fruit flies, in which an AMPK-like enzyme’s phosphorylation of specific sites on the tau protein led to a cascade of further phosphorylations and the degeneration of nerve cells. The scientists confirmed that one of these sites, S262, is indeed phosphorylated by AMPK. They then showed that this specific phosphorylation of tau accounts to a significant extent for amyloid beta’s synapse toxicity.

“Blocking the phosphorylation at S262, by using a mutant form of tau that can’t be phosphorylated at that site, prevented amyloid beta’s toxic effect on spine density,” Mairet-Coello said.

The result suggests that amyloid beta contributes to Alzheimer’s via AMPK, mostly as an enabler of tau’s toxicity. Mairet-Coello, Polleux and their colleagues are now following up with further experiments to determine what other toxic processes, such as excessive autophagy, are promoted by AMPK overactivation and might also contribute to the long-term aspects of Alzheimer’s disease progression. They are also interested in the long-term effects of blocking AMPK overactivation in the J20 mouse model as well as in other mouse models of Alzheimer’s disease, which normally develop cognitive deficits at later stages. “We already have contacts within the pharmaceuticals industry who are potentially interested in targeting either CAMKK2 or AMPK,” says Polleux.
Leta Lindley: Raising the Profile of a Life-Threatening Disorder for Children

Leta Lindley has had a long and successful career in golf. Leta, who started playing golf at the age of 9, played collegiate golf at the University of Arizona, where she was a four-time All-American and three-time Academic All-American, and at the time held the NCAA record for lowest 54-hole score. After 18 years on the LPGA Tour and ranking among the top 60 all-time LPGA money winners, she retired last summer to focus on being a mom. During her career, her husband, Matt Plagmann, caddied for her, and her son Cole, and daughter Reese traveled with the couple. Leta is one of only five LPGA players to win a tournament after giving birth.

While her family and golf are her two legacies, Leta, a resident of Palm Beach Gardens, Florida, is working on a third—she serves as Tournament Director and the face of the Leta Lindley Prader-Willi Classic. The Classic, held each year at PGA National Resort & Spa, features Leta, who lives nearby, and 25 of her famous “sisters,” LPGA stars who step up and join her to play in support of a research fellowship at Scripps Florida on Prader-Willi Syndrome, a little-known genetic disorder, affecting children.

The fellowship is under the direction of Roy Smith, Ph.D., Founding Chairman of Scripps’ Department of Metabolism and Aging. It is focusing on the development of a therapeutic intervention as a potential treatment of Prader-Willi Syndrome.

Leta has no connection to the disease, but she has decided it deserves her support. It was after she gave birth to her healthy, second child Reese several years ago that she met Josie Levine, now 10, and other children and families affected by Prader-Willi.

Prader-Willi Syndrome affects one in approximately 12,000 births. It inhibits growth, intelligence, muscle development, and affects behavior. The most recognizable symptom of the life-threatening disorder is an inability to recognize when one has eaten enough and an insatiable hunger; as a result, many of those afflicted can’t recognize feeling full and become obese, and the rest need constant monitoring in the presence of food. There is no cure and those with Prader-Willi Syndrome require 24 hour care for their entire lives.

Grateful for her blessings, Leta made a commitment to help the children and their families. “Being a mother of two small children, I couldn’t imagine the daily challenges,” said Leta. “When I thought about what Josie and these children deal with, I thought I could do more than just help out— I could turn what was a small “family-and-friends” golf tournament into an LPGA event and increase turnout. This isn’t a cause like breast cancer or diabetes that gets lots of attention; it needed someone who could help raise awareness and money.”

“It breaks my heart that family members must deny the pleas of these children who are told that they can’t eat because it might kill them,” said Leta. “I can’t imagine what it must be like to have a child who struggles with this daily.”

When Leta played in her first charity event for Prader-Willi five years ago, it raised about $10,000 as a “friends-and-family fundraiser.” It was there that, she was paired with Ira Levine, Josie’s grandfather, who was frustrated with the lack of information and available treatment options for those with Prader-Willi. “It was overwhelming to hear a grandfather who couldn’t make things better for his granddaughter.”

Josie maintains a strict 1,200-calorie diet. She’s one of the many children with the disease who have captured Leta’s heart. With Leta’s support, this year’s tenth annual tournament raised $240,000.

Leta considers herself an underdog, so it’s only fitting that she is the champion of an “underdog” cause. “I’m the girl that was never going to do it. I would never get a college scholarship; I would never win a college tournament. I would never get my LPGA card, let alone keep it.”

Leta is hopeful for a cure for the disease. It is people like Leta that make the future brighter for all those battling Prader-Willi Syndrome. “I think the research at Scripps is advancing in a good direction. I know the families, event participants, and myself are encouraged and excited—and we’re glad that the research is taking place locally,” said Leta.

“Having the opportunity to use my golf for something better and bigger and helping children that have Prader-Willi Syndrome, that has been my dream,” said Leta. “I’ve had two healthy children and have had this God given talent my whole life. I want to give something back. It’s pretty easy to be involved—I’ve fallen in love with these families.”
Ian Wilson: Major Strides Move Universal Flu Vaccine and HIV Vaccine Closer to Reality

Over 30 years ago, TSRI Professor Ian Wilson, then a scientist at Harvard, decided to take a trip to the San Diego Zoo. On the way to the zoo, he visited Richard Lerner, who was President of TSRI at the time. Ian never made it to the zoo, but he did accept a job at TSRI, and has never looked back. In fact, he is looking forward through his ultimate goals of a universal vaccine for the flu and a vaccine for HIV.

“I love working here,” said Ian. “It’s a place where you can work on anything you want and have the support of the President and the rest of the administration.”

Ian, who is chair of the new TSRI Department of Integrative Structural and Computational Biology and a member of the International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Center at TSRI, specializes in the use of X-ray crystallography and other techniques to determine precisely where and how broadly neutralizing antibodies bind to their viral targets. He and his colleagues are using computational methods to design new antiviral proteins not found in nature, but capable of targeting specific surfaces of flu and HIV virus molecules.

Influenza is a common viral infection of the lungs that affects millions of people annually and is a leading cause of death in the United States, contributing to around 50,000 deaths per year. Serious influenza outbreaks such as the deadly “Spanish flu” of 1918 have occurred when a virus adapted to birds jumps directly into humans or reassorts and infects another species, such as the pig, and then jumps into humans. Similar outbreaks to the “Spanish flu” occurred with the Asian Flu in 1957 and the Hong Kong Flu in 1968. These three major human influenza pandemics have devastated the human population, killing around 50 – 100 million people worldwide.

The most recent influenza outbreak, dubbed the “swine flu” by the media due to its recent origins in pigs, was first reported in Mexico in 2009. The virus spread worldwide, and contributed to at least 16,000 deaths according to the World Health Organization.

Annually changing flu vaccines with their hit-and-miss effectiveness may soon give way to a single, near-universal flu vaccine, largely due to Ian’s work. Current influenza vaccines also provide little or no protection against unforeseen strains.

“This is very exciting and addresses a major global health threat,” said Ian. “Such a flu vaccine could be given to a person just once and would act as a universal protectant for most subtypes of influenza, even against pandemic viruses.”

Ian’s team at TSRI along with scientists at Crucell Vaccine Institute in the Netherlands has been pioneers in finding broadly neutralizing human antibodies that can provide broad protection against Influenza A and influenza B virus strains. The isolation of these new broadly neutralizing antibodies paves the way for researchers to develop a universal antibody-based flu therapy for use in severe infections or to protect hospital staff during an outbreak.

“To develop a truly universal flu vaccine or therapy, one needs to be able to provide protection against influenza A and influenza B viruses, and we now have broadly neutralizing antibodies against both,” said Ian. “We have the potential to protect people against most influenza viruses. This is an exciting time as the technology has improved tremendously, opening up new opportunities.”

One of Ian’s newly discovered antibodies from Crucell appears to protect essentially against all influenza B and influenza A strains. “It’s the only one in the world that we know of that has been found to do this,” said Ian.

In the HIV area, Ian and his colleague, TSRI professor Dennis Burton, who is also scientific director of the International AIDS Vaccine Initiative’s (IAVI) Neutralizing Antibody Center and the Scripps Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID), based at TSRI, were the first to appreciate the importance of characterizing broadly neutralizing antibodies to neutralize the virus. They have uncovered surprising details of how a powerful anti-HIV antibody grabs hold of the virus, highlighting a major vulnerability of HIV and suggesting a new target for vaccine development.

“We can now start to think about constructing mimics of these viral structures to use in candidate vaccines to prevent AIDS,” said Ian.

continued on page 6
Since the 1990’s, Ian and Dennis have been searching for such “broadly neutralizing” antibodies against HIV – antibodies that work against many of the various strains of the fast-mutating virus – and have now found more than a dozen. Researchers hope to use the knowledge of these antibodies’ binding sites on HIV to develop vaccines that stimulate a long-term – perhaps lifetime – protective antibody response against those same vulnerable sites.

Ian’s studies have included some integral funding from philanthropy, much of it from the Skaggs family. “Philanthropic funding has been very important to us,” said Ian. “Things are changing and we can’t rely on the National Institutes of Health anymore for all of our support. We need to look for other opportunities. The Skaggs funding, as well as the funding and collaboration with the International AIDS Vaccine Initiative and the Crucell Vaccine Institute has been very important to us.”

One theme of the center’s research is the exploration of the human “microbiome,” the collection of microbes that inhabit specific environments, such as the human digestive tract.

“Interactions of bacteria with the human body are profound and have a significant impact on maintenance of general human health,” said Ian. “In addition, they are associated with obesity, inflammatory bowel disease, Crohn’s disease, diabetes, and certain cancers.”

Ian is well-known on campus for his support of TSRI’s graduate students. In 2010, he received a new award, named after the first dean of TSRI’s graduate program, “Bernie” Gilula. Ian was cited for his roles in developing the graduate program’s initial curriculum, organizing a course in biophysics, and acting as faculty advisor for the Skaggs Oxford joint Ph.D. – D.Phil. program.

“Io has been tremendously rewarding for me to see each student develop and flourish during their graduate education and subsequent careers,” said Ian.

Ian is also proud of being named as TSRI’s 2012 Outstanding Mentor. He has mentored more than 100 graduate students and postdoctoral fellows, many of whom now hold top positions in academia and industry around the globe—14 of whom wrote letters in support of his nomination as Outstanding Mentor.

The letters emphasized Ian’s merits as both an accomplished, highly cited scientist and compassionate, thoughtful mentor, who also exhibits a whimsical sense of
humor. The letters spoke repeatedly of his ability to teach excellence in science, his genuine concern for the welfare of his lab members, and his active support of lab members’ careers, including making phone calls to personally advocate for current and former lab members pursuing coveted job offers.

According to one of the letter writers, “Every time you had a big talk coming up, Ian will sit with you and go through it slide by slide. He would come in on weekends, bring fresh fruit from the farmer’s market, and sit and talk with you about your research and offer you some star fruit . . .

He diffused almost all the stress of my thesis defense by asking me what kind of cake I wanted at the party afterwards and then by showing up and sitting in the audience in a silly-looking plastic Red Sox helmet (we’re both Boston fans). While giving my public defense, I could not even look in his direction for fear I would burst out laughing.”

Ian is also proud of his standing as a fellow of The Royal Society, a 350-year-old independent academy in the United Kingdom promoting the natural and applied sciences. Scientists in The Royal Society follow in the footsteps of early fellows such as Isaac Newton, Robert Boyle, and Robert Hooke and embody the spirit of enquiry dedicated to the relief of man’s estate on which The Royal Society was founded.

Additionally, Ian is a corresponding fellow of the Royal Society of Edinburgh, Scotland’s National Academy of Science and Letters, established in 1783. Ian follows in the footsteps of distinguished predecessors including Sir Walter Scott, Charles Darwin, and Albert Einstein.

Ian Wilson is an accomplished scholar, mentor, and is driven day to day in his quest to combat influenza and AIDS.

“For this to be of value in Third World countries we need to morph this biomarker into something that’s inexpensive, simple to use, tolerant of extreme temperatures and portable — basically distilling our finding to a test that can be carted around in a backpack,” said Janda. “This new gift will make that possible.”

A leading cause of vision loss, Onchocerciasis infections are transmitted among humans by river-dwelling blackflies in tropical regions. The vast majority of cases occur in sub-Saharan Africa, although pockets of endemic infection exist in Yemen and in Central and South America. The major symptoms of the disease, including blindness, result from the spread of O. volvulus “microfilariae” — early-stage larval worms — to the eyes and other tissues, where they trigger damaging inflammatory reactions.

Mass treatment campaigns, begun in the 1990s, have used the anti-worm drug ivermectin, as well as the antibiotic doxycycline, which kills a symbiotic bacterium within the worms. But Onchocerciasis treatment is seldom effective immediately, and often spares adult worms. The latter can remain in protected nodules under the skin of a patient and secrete microfilaria for a decade or more.

Current diagnostic methods include the painful cutting of “skin snips” from patients for microscopic analysis and an ELISA antibody test for microfilariae, which may yield positive results even for non-active infections. Health agencies need better diagnostic methods to track the progress of Onchocerciasis treatment campaigns and to wisely monitor the use of ivermectin and doxycycline to reduce the risk of resistance.

Janda envisions the new diagnostic test, which he hopes to develop over the next two years, as a simple, accurate and painless urine dipstick test, much like a home pregnancy test. The diagnostic would indicate the amount of the O. volvulus biomarker present in the sample to guide treatment decisions and assist global health leaders in their quest to eradicate the disease.
Partners

The Frontiers in Science event series continued on the La Jolla campus in March with a presentation by Associate Professor Peter Kuhn on “Personalizing Cancer Care.” The lunchtime series educates donors on the latest scientific discoveries in health topics that relate to them through presentations from prominent TSRI scientists. Approximately 50 donors came to listen and learn as Dr. Kuhn explained his latest research efforts on circulating tumor cells that spread throughout the body, as well as his latest breakthrough – a “next generation” blood test to detect metastatic cancer – which would give physicians a faster and better way to adjust treatments to a variety of cancers. Pictured at the event are longtime TSRI donors Bill and Shirley Kimmich.

House Majority Leader Eric Cantor (R-VA, right) met recently with TSRI President Michael Marletta on the Scripps California campus. The meeting was followed by a roundtable discussion, sponsored by the California Healthcare Institute, during which local biotech and TSRI executives offered Cantor perspectives on federal programs, funding and proposals to spur innovation.

Contact Us:

- For more information about TSRI, visit our web page at www.supportscrippsresearch.org
- To learn more about supporting TSRI’s cutting-edge research, please contact:

  **CALIFORNIA**
  (858) 784.2037 or (800) 788.4931
  burfitt@scripps.edu

  **FLORIDA**
  (561) 228.2013
  abruner@scripps.edu