Scripps Research Institute Dedicates Dorris Neuroscience Center

The Scripps Research Institute dedicated the Dorris Neuroscience Center on May 25, officially launching the newly consolidated center and honoring the woman who has supported work at the institute for many years. Her gifts include an endowment to support neuroscience research.

“We are grateful to Helen L. Dorris for her continuing generosity,” said Richard A. Lerner, president of Scripps Research, “as well as for her foresight to provide for research in the years to come. I have no doubt that scientific investigations at the Dorris Neuroscience Center will deepen our understanding of the nervous system, and lead to breakthroughs in the treatment of neurological diseases.”

Professor Ulrich Mueller, director of the new center, said, “Thanks to Helen Dorris’s benevolence, the new neuroscience center will make it possible for us to focus and renew our efforts to make an impact in one of the greatest challenges ever faced by science—understanding the human brain. We intend to lead the way in this research that will reveal novel strategies and targets for the treatment of nervous system disorders.”

Helen Dorris—a mental health advocate and San Diego State University professor emeritus—made a significant gift to launch the new center through The Harold L. Dorris Neuroscience Foundation, named in her brother’s honor. The new Dorris Neuroscience Center also consolidates and builds on two previous centers that she had made possible at Scripps Research, the Harold L. Dorris Neurological Research Center and Helen L. Dorris Institute for the Study of Neurological...
and Psychiatric Disorders of Children and Adolescents. Dorris is a resident of San Diego.

The new Dorris Neuroscience Center brings together scientists early in their careers with established researchers in the field, and provides them with high-end imaging technology and state-of-the-art genomic and genetic research tools to advance their research programs. The laboratories of many of the center’s investigators are located in the Harold L. Dorris Neuroscience Center Building (previously known as the ICND building), a 53,000-square-foot structure with cutting-edge facilities situated on the east side of the Scripps Research California campus.

Using diverse biological, biophysical, and chemical approaches, the researchers at the new center conduct investigations that fall within two general areas of neuroscience: sensory systems (including smell, hearing, and pain) and neuronal circuitry (including the systems that govern memory). Stem cell research is a further important component of the program. In addition to Mueller, the center’s faculty includes: Assistant Professor Kristin Baldwin, Professor Jerold Chun, Professor Hollis Cline, Assistant Professor Boaz Cook, Professor Ben Cravatt, Assistant Professor Anton Maximov, Associate Professor Mark Mayford, Professor Ardem Patapoutian, and Associate Professor Lisa Stowers.

“Members of the Dorris Neuroscience Center explore some of the most fundamental questions in neuroscience research,” said Mueller. “How do stem cells differentiate to generate neuronal circuits? How do sensory systems process information? How do we store and retrieve memories? What are the mechanisms that lead to sensory impairment such as hearing loss or to debilitating diseases such as schizophrenia, autism spectrum disorder, and depression? We are also looking toward useful strategies for the treatment of these diseases.”

In addition, the Dorris Center for Neuroscience will sponsor three Helen Dorris Scholars, an annual student award, a number of summer student internships, and a distinguished lecture series.

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“The Kellogg School offers both an interesting curriculum and the opportunities to join stellar research laboratories for thesis work,” said Dean James Williamson. “Graduate work at Scripps is a special opportunity, and many of the features of our program are different than at a traditional university. Our goal is to provide the most conducive environment to enable students to make important discoveries as a stepping stone for their careers.”

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The Scripps Research graduate program was launched in 1989. Since then, the program has grown rapidly in both size and reputation, now consisting of more than 200 students of the biological and chemical sciences. In 2002, it was named the Kellogg School of Science and Technology, in honor of philanthropists Janet R. (“Jean”) Kellogg and W. Keith Kellogg II. Alumni of the program from both the La Jolla, California and Jupiter, Florida campuses have gone on to hold prominent positions in academia and industry.

The U.S. News & World Report periodically reviews schools, including undergraduate institutions and community colleges, across the country. The previous rankings of Scripps Research published in 2002 placed the program sixth in chemistry and ninth in the biological sciences.

The new rankings were based on a survey of academics in each field conducted during the fall of 2009. The questionnaires, sent to department heads, deans, directors of graduate studies and other individuals in each discipline, asked individuals to rate the quality of the program at each institution. In addition, respondents were asked to nominate programs that had excellent offerings in certain specialty areas. Those programs that received seven or more nominations were listed, in order of the number of nominations received.

Other metrics corroborate the school’s high standing. An index of graduate program faculty published in The Chronicle of Higher Education in 2007 ranked the Kellogg School as best in the nation in biophysics, second in immunology, and seventh in biochemistry.
Scientists from The Scripps Research Institute have provided an answer to the 40-year-old mystery of how certain genetic mutations lead to Type 1 diabetes. This new molecular understanding could lead to novel therapies for Type 1 diabetes and other autoimmune diseases.

“People have been looking for the mechanism linking HLA and autoimmunity for 40 years,” said Scripps Research Professor Luc Teyton, who led the study with Scripps Research Professor Ian Wilson. “This study provides a big leap forward in understanding and suggests a critical new target to intervene in type 1 diabetes.”

Teyton notes that his lab has been trying to solve the mystery of autoimmune mechanisms and related conditions like celiac disease for some 25 years.

This new study focuses on Type 1, or insulin-dependent diabetes, a rapidly progressive disease of the young that leads to high blood sugar, coma, and death if not treated with replacement insulin.

Type 1 diabetes occurs when the body’s immune system attacks insulin-producing b cells in the pancreas. Without insulin, the glucose in the bloodstream increases dramatically; early symptoms are unusual thirst, increased output of urine, fatigue, and unusual hunger accompanied by weight loss.

Currently, the only therapy available is to compensate for the destruction of the body’s insulin-producing cells by injecting insulin on an ongoing basis.

While genes predispose people to many different types of diseases in many different ways, specific genetic variations are an especially strong predictor of the development of type 1 diabetes. Three genetic variations in particular (HLA-DQ2, HLA-DQ8, and HLA-DR0405)—all located in the region of the genome called HLA for “human leukocyte antigen”—are known to dramatically increase risk of coming down with the condition.

These three genes encode molecules that present peptides (protein fragments) to the body’s T cells. T cells then determine whether the peptide being presented is dangerous and needs to be eliminated from the body—as in the case of foreign invaders such as bacteria or viruses—or whether the peptide is “self,” part of the host and something the immune system needs to leave alone. However, in the context of type 1 diabetes, T cells aggressively attack the body’s own cells.

The scientists wanted to know on a molecular level how mutations in the immune surveillance machinery could lead to type 1 diabetes.

“We were interested in trying to understand why certain MHC molecules (which are molecules in mice analogous to HLA molecules in humans) are linked to autoimmune disease, particularly type 1 diabetes,” said Research Associate Adam Corper of the Wilson lab, who was first author of the paper with Kenji Yoshida of the Teyton lab. “In particular, we wanted to know why a single residue at position 57 on the β chain of HLA molecules seems to be linked to the disease.”

In the new research, the team used a series of structural and biophysical studies to answer that question.

Previously, the Teyton and Wilson labs had determined the structure of a “diabetogenic” MHC molecule and found that mutations to position 57 caused only subtle changes. It did not, as some had speculated, cause the molecule to become unstable and non-functional.

Now, in the new study, the researchers found that diabetes-causing mutations changed the charge at one end of the MHC peptide-binding groove. In individuals not predisposed to type 1 diabetes, MHC molecules usually have a negatively charged residue at position 57. In contrast, disease-causing MHC molecules have a neutral residue at position 57 and consequently the surrounding region is more positively charged.

The result of this molecular change was that the mutated MHC molecules selected a unique subset of T cells that bound to it strongly, with “higher affinity.” These T cells may overreact and potentially misidentify “self” peptides as dangerous rather than harmless.

“We found that the MHC region around position 57 can be seen by the T cell receptor,” said Teyton. “That’s the big novelty of the paper—for the first time, we show that it is not only essential for peptide binding, but also critical for the selection of T cells. Finally, we have an idea of why those particular MHC molecules are associated with disease.”

Corper added, “What we have here is potentially a way of breaking ‘tolerance’—the mechanism where the immune system doesn’t respond to self. Obviously, if that breaks down you get autoimmune disease.”

The team is now investigating potential antibody or small molecule therapies that could target and correct mutated MHC.
After losing her husband Saul after almost fifty years of marriage, Theresa Esman created the Saul and Theresa Esman Foundation to zero in on those diseases that are the biggest killers. Scripps Florida is one of several key beneficiaries of the generosity of Theresa and her foundation.

Saul was a tremendous man of character, personality, perseverance, hard work, and entrepreneurial spirit. He built an extremely successful sporting goods business in Pittsburgh, and was always loyal and supportive of those who worked for him. In fact, Theresa was one of those employees.

Saul sold his business in 1979, and he and Theresa settled in South Florida, giving lots of their hard-earned income to charity. Theresa, still going strong, now resides in beautiful Bal Harbour, Florida.

“My husband wanted the benefits of his hard work to help people. We fund research that will be good for mankind long after I’m gone,” said Theresa.

The Saul and Theresa Esman Foundation, funds a spectrum of work in diseases such as diabetes, Alzheimer’s, Parkinson’s, cardiovascular disease/stroke, and cancer.

Two years ago, when few people in South Florida wanted to step to the philanthropy plate due to the Madoff scandal, Theresa was the first to fund the American Heart Association’s Children Reach-Out Initiative which focuses on building awareness and preventing childhood obesity, as well as increasing support to those children whom already have heart disease.

“Theresa has a great heart. She deserves all the credit for the funding and support she gives to charities. Despite the losses incurred by South Floridians due to the Madoff scandal, she still stepped up with the American Heart Association gift,” said Murray Levin, Executive Director of the Saul and Theresa Esman Foundation, as well as a world champion weightlifter, President of the Pan American Games weightlifting sport for 20 years and United States President for 13 years, the founder of women’s weightlifting 30 years ago, and a World War Two veteran.

Theresa also supports the American Diabetes Association.

“It used to be that people started getting diabetes in their 40’s and 50’s,” said Theresa. “The whole picture is changing and it’s scary.”

On her funding of the Alzheimer’s Association, Theresa said, “It’s so sad when people share their lives together and suddenly a spouse does not know her partner. It’s hard to keep from breaking down.”

Theresa has made two major annual gifts to support Parkinson’s disease research in the laboratory of Dr. Phil LoGrasso at Scripps Florida, via the Saul and Theresa Esman Foundation.

“We were so pleased with Scripps’ work that we stepped forward again without even being asked,” said Murray. “Scripps Florida is near and dear to the foundation’s heart. It is involved in so many different areas. We are proud to be a contributor to Scripps.”

“For us, this is not simply an annual thing,” said Murray. “We meet with the executives of the charities during the year and we stay on top of their progress.”

“The generous gifts from the Saul and Theresa Esman Foundation allow us to pursue novel work in developing neuroprotective agents to treat Parkinson’s disease, and to better understand the underlying mechanisms which cause the disease,” said Phil LoGrasso.

“The funding goes to support a postdoctoral fellow and is extremely valuable because it helps us pursue groundbreaking research that is needed to produce preliminary data for additional National Institutes of Health funding.”

“Mrs. Esman’s gentle and elegant manner is in keeping with the supportive nature of her gift, and her thoughtfulness provides great encouragement in our work.”

“The footprints we leave behind are our legacy,” said Murray. “We are excited that Dr. LoGrasso is working hard on the diseases that are destroying our people and wish him the best of success. We’ve been really happy with the progress he’s making, and see this as a long-term relationship.”

“We believe in what you’re doing,” said Theresa. “None of us knows what’s going to happen to us down the road, and we’re all sadly touched by diseases in our family and friends—medical research provides hope for us all,” said Theresa.

Theresa Esman holds a Scripps Florida Alberello, an historic Italian apothecary jar, presented to her in appreciation for her major gifts.
As an undergraduate biochemistry student at the University of California, Berkeley, in the late 1980s, the mentally ill homeless people that Beth saw on the street every day reinforced her interest in studying pharmacology and the effects anti-psychotic drugs, which are used to treat psychiatric illnesses. As a postdoctoral fellow at Scripps Research in the 1990s, her research interests expanded to include neurodegenerative disorders, when a colleague in her lab discovered she was at risk for Huntington's disease.

Today, as an Associate Professor at Scripps Research on the California campus, Beth continues to work diligently to investigate the role of genes in brain-destroying diseases, such as schizophrenia. Her research aims to understand the nature of gene dysfunction in these disorders in order to provide a basis for improved therapeutics and disease prevention.

The debilitating psychiatric disorder, schizophrenia, which means “fragmented mind,” usually begins in the late teens or early adulthood. Symptoms include delusions, hallucinations, bizarre behavior, depression, social withdrawal, apathy, and poor communication skills. These symptoms make affected individuals unable to function in society, resulting in a huge community burden. It is a common mental illness, affecting close to 1% of the general population. While the outcome varies among individuals, the course of illness is one of frequent relapse and persistent dysfunction that lasts throughout one’s lifetime.

“In general, schizophrenia remains a poorly diagnosed, poorly understood, and inadequately treated illness, one that is especially heartbreaking because it strikes people in their teens and early 20s. It’s a horrible disease for individuals and their families that can often end in suicide at an early age,” says Beth. “Many genes contribute to the cause of the disease, making it extremely complex to study, and better pharmaceuticals are needed — the pharmaceuticals for schizophrenia today are generally no better than those developed fifty years ago.”

Researchers are actively working to identify the direct causes of schizophrenia, likely rooted in interactions between genes and the environment resulting in abnormal gene expression in the central nervous system. Scientists have been studying expression changes in schizophrenia on an individual gene basis, yet this strategy has explained only a portion of the genetic risk.

In recent work, Beth and her team of researchers took a novel approach to this problem, performing a gene network-based analysis using microarray technology that enables analysis of up to 40,000 genes at once. The work revealed surprising new insights into how gene regulation and age play a role in schizophrenia and how schizophrenia may develop.

The group analyzed gene expression from the prefrontal cortex, a region of the brain associated with schizophrenia, and sampled post-mortem from normal individuals and schizophrenia patients ranging from 19 to 81 years old, some who only had the illness for two or three years. However, instead of just looking at genes individually, Beth and her colleagues considered interactions between genes, as well as groups of genes that showed similar patterns of expression, to identify dysfunctional cellular pathways in schizophrenia.

“In the end, nothing would make me happier as a scientist than to have a role in making it possible for people with schizophrenia to be able to function better in society, and to contribute to a possible cure for Huntington’s, allowing patients to live a full life,” said Beth Thomas.

—Associate Professor Beth Thomas

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developmental hypothesis of schizophrenia, which states that one or more pathogenic “triggers” occur during a critical period of development to increase risk for the disease. Specifically, this work indicates that abnormal gene expression in developmentally related genes might be a significant pathogenic trigger, occurring over a broader time-scale than expected. “Rather than a pathological trigger occurring at a critical developmental time point,” said Beth, “the trigger is ongoing throughout development and aging. This suggests a bigger window of opportunity for early treatment.” She added, “Although it is clear that identifying new drugs to treat schizophrenia is essential, these studies reveal how the mode of treatment may improve outcome.”

Studies have shown that treatment soon after initial diagnosis of schizophrenia results in good outcome. Although prophylactic treatment in schizophrenia is controversial, it is possible to identify those individuals at a high risk for developing the disease, based on family history and particular symptoms that appear several years prior to disease onset. Beth noted that the new study supports early intervention and treatment of schizophrenia prior to official diagnosis, in which therapeutic approaches would be aimed at averting gene expression changes occurring early on.

“Our studies underscore the idea that early intervention is critical and could alter the course of disease,” Beth says.

Another important finding from her recent studies is that the aging process in schizophrenic patients appears to be quite different from normal subjects. In particular, Beth found that genes related to inflammation were expressed differently in older patients compared to young patients and that this age difference was not found in normal subjects. “This may translate into a simple application of personalized medicine, which could be to specifically tailor medications to the age of the patient” says Beth. These findings have enormous implications with regards to anti-inflammatory treatments, which have recently emerged as important adjuncts to standard antipsychotic drug therapy. Anti-inflammatory agents may prove to very useful to young patients with schizophrenia, but not older patients with chronic illness. This approach, she added, could be applied to several other neurological disorders as well.

Beth’s group was the first in the world and is still the only group to tease apart schizophrenia on a molecular level according to stage of illness and age. Using the post-mortem brains of schizophrenia patients allowed Beth to study various aspects of early-stage illness, as well as chronic disease, in the central nervous system itself where the disease is actually happening, as opposed to looking at blood samples. Post-mortem brain samples from younger subjects are often difficult to obtain as these patients often suffer a tragic death or suicide, meaning the parents are less willing to donate their sons or daughters brains to science. This is the main reason that most studies in the past have focused on subjects with chronic illness.

Beth’s interest in Huntington’s disease – which is characterized by progressively worsening involuntary movements, loss of intellectual faculties, emotional disturbances and premature death – was initially piqued by a Scripps Research friend and colleague who was at significant risk because her mother had passed away from the disease.

Accompanying her friend to support group meetings only intensified Beth’s resolve to study Huntington’s disease, the most common inherited neurodegenerative disease. About one in 10,000 Americans has Huntington’s disease and 150,000 people are believed to be at risk, meaning that one of their parents inherited the disease, giving them a 50 percent chance of developing it as well.

“It was unbelievably moving to witness how Huntington’s disease rips apart those who have the disease, those at risk, and their families,” says Beth. “I felt I had to do whatever I could to help better understand this terrible disease that strikes people when they are relatively young – in their 40s or even younger, and still in the prime of their lives.”

There is no cure for Huntington’s disease, or even treatments that can reverse or slow progression of the devastating movement deficits and cognitive dysfunction that occur with the condition. But Beth and her colleagues have developed an agent that has shown dramatic therapeutic efficacy in experimental mice, and with minimal toxicity.

Beth and her colleagues work with “transgenic” mice – those whose DNA has been altered so that the mouse exhibits the characteristics of Huntington’s disease – to try to understand the genetic basis for the disease. Using microarray technology, as in her schizophrenia studies, she has identified many genes expressed in the striatum of the transgenic mice that seem to be involved in both early and late stage neurodegeneration.

Because the brains of these Huntington’s disease transgenic mouse models show high levels of abnormal gene expression, Beth, in collaboration with Scripps Research

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A patient diagnosed with cancer has a dysfunctional immune system either because of the tumor or the treatment being used to eradicate the tumor. These designer lymph nodes will help to rebuild a patient’s immune system in order to help fight disease. Researchers also hope to increase the potency of vaccines.

“We believe we will no longer be held hostage by what Mother Nature has given us with respect to an immune system,” said James Mulé, executive vice president of applied research at Moffitt Cancer Center, which is located in Tampa. “We anticipate we will be able to create fully-functioning, designer lymph nodes at will in the human body.”

Mulé is partnering with John Cleveland, chair of the Department of Cancer Biology, and Juliana Conkright, senior staff scientist, at Scripps Florida, the Jupiter campus of The Scripps Research Institute. The Scripps Florida scientists will be using high-throughput screening technologies to rapidly select the candidate genes to use in creating the human lymph nodes.

“Our collaborative efforts hold the real promise of restoring anti-tumor activity to the immune system of cancer patients, and could lead to cures for some cancer types,” said Cleveland. “It is also a perfect example of the creative, state-of-the-art science being driven by investigators at Moffitt and Scripps and the power of collaboration between the two institutes in moving biomedical science from the laboratory to the patient.”

The creation of these designer lymph nodes is not limited to cancer. The team plans to expand their use to other areas to boost immunity against a variety of infectious diseases and/or to improve the functions of the immune system during aging.

A clinical trial in melanoma is currently under way at Moffitt using one of the first candidate genes as a primitive lymph node. Twelve patients are presently enrolled.
A W A R D S  A N D  H O N O R S

Peter Vogt Wins Szent-Györgyi Prize

P eter Vogt, professor at The Scripps Research Institute, has won the Szent-Györgyi Prize for Progress in Cancer Research. The annual prize, now in its fifth year, is awarded by the National Foundation for Cancer Research (NFCR) to scientists who have contributed outstanding, substantial research to the fight against cancer and whose accomplishments have helped improve treatment options for cancer patients.

“Dr. Vogt’s fundamental basic science discovery of cancer-causing genes in retroviruses shed the first light on the genetic paradigm that now dominates our understanding of cancer development in humans,” said Ronald A. DePinho, chair of the Szent-Györgyi Prize Selection Committee and last year’s recipient. “His groundbreaking work has yielded several of the most important targets in cancer therapy. We are honored to present this coveted award to an individual of iconic stature.”

The prize was presented on March 16 during the 21st annual Cancer Progress Conference.

Claes Wahlestedt Elected Chair of FL CURED, Appointed to Research Advisory Council

S cribps Research Professor Claes Wahlestedt has been elected chair of The Florida Center for Universal Research to Eradicate Disease (FL CURED), a state-wide organization that works to improve coordination, information sharing and reduce duplication within Florida’s biomedical research enterprise. Governor Charlie Crist has also appointed Professor Wahlestedt to the Biomedical Research Advisory Council (BRAC) of Florida.

Frontiers in Science Event

S cribps Research continued its Frontiers in Science lecture series for donors and friends in April at the Hyatt Regency La Jolla at Aventine. At the event, Scripps Research Professor Benjamin Cravatt, Ph.D., spoke to over 120 Scripps Research contributors and friends on “From Basic Medical Research Discoveries to New Pharmaceutical Avenues that Relieve Suffering – The Critical Path.” Pictured at the event are Scripps Research California Council Chair Katherine Kennedy, Benjamin Cravatt, Ph.D., and Scripps Research trustee Thomas Insley.

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