

SCRIPPS DISCOVERS

Accelerating Discoveries, Saving Lives

A Newsletter for Philanthropists Published Quarterly by The Scripps Research Institute

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DONOR PROFILES

Conquering Fragile X Syndrome

> Encouraged by the enthusiasm of Harris Hollin, a retired Palm Beach businessman, Scripps Florida professor **Claes Wahlestedt, M.D., Ph.D.**, and his colleagues, have discovered a new gene involved in Fragile X syndrome, a condition that often shares many symptoms of autism.

The discovery may lead to new tests or treatments for several neurological disorders.

The study on the new gene — which the Scripps Research scientists have dubbed FMR4 — was published January 23 in the journal *PLoS ONE*.

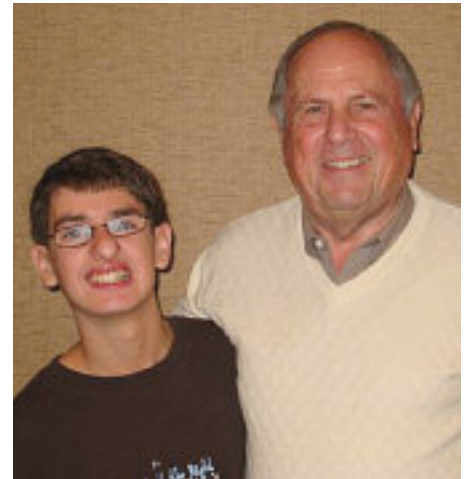
“FMR4 is a novel gene that is located in the same chromosomal neighborhood as FMR1, a well established causative gene in Fragile X

syndrome,” said Wahlestedt. “Like FMR 1, FMR4 is silenced in Fragile X patients and upregulated in FXTAS (fragile X-associated tremor/ataxia syndrome), a disease that resembles Parkinson’s disease. Our discovery could lead to the development of new diagnostic tests or even to novel therapies for these defects.”

When Scripps Research came to South Florida in 2004, Fragile X wasn’t on the research organization’s radar screen. But Hollin approached Scripps Research leaders to enlist their help.

Fragile X is a genetic disorder that is the most common inherited cause of mental retardation and learning disabilities.

Hollin’s grandson, Matthew, has Fragile X syndrome. “I never even heard of Fragile X,” said Hollin. “When I heard the news, I told my son and his wife that I would do anything I could to help.” In 1999, Hollin founded the Palm Beach-based Conquer Fragile X Foundation (CFX), a national nonprofit organization that raises awareness and money to find a treatment for the disorder.



Harris Hollin with his grandson Matthew

Fragile X syndrome affects thousands of patients worldwide with severe learning disabilities, often accompanied by anxiety disorders, obsessive-compulsive behavior, and attention deficit hyperactivity disorder. There are currently no therapeutic treatments available for fragile X syndrome.

More than 16 years ago, scientists linked fragile X syndrome to inactivation of FMR1 gene expression, leading to the lack of a protein known as the fragile X mental retardation protein, now considered to be critical for neuronal function. Until the current study, no other functional gene other than FMR1 had been shown to be inactivated in the disorder.

While Hollin had sponsored research elsewhere, particularly in Israel, he was looking for a fresh set of eyes and a new approach.

With a background in the pharmaceutical industry, Hollin’s group donated \$125,000 to support

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Institute is Considered a Key in the Full Court Press to Stop Friedreich's Ataxia

> Friedreich's ataxia (FRDA) is a rare, genetic, neurodegenerative, multi-system, life-shortening disorder. About one in 50,000 people in the United States have Friedreich's ataxia. Onset of symptoms is usually between the ages of 5 and 15, sometimes even earlier and sometimes significantly later.



Ron Bartek (right) with Raychel and Keith

Symptoms of Friedreich's ataxia include muscle weakness and loss of coordination (ataxia) in the arms and legs; vision impairment, hearing loss, and slurred speech; aggressive scoliosis (curvature of the spine); diabetes mellitus or carbohydrate intolerance; and a serious heart condition (enlarged heart – hypertrophic cardiomyopathy).

These symptoms reflect the death of cells in certain parts of the body. The mental capabilities of people coping with Friedreich's ataxia, however, remain completely intact. For most, progressive loss of muscle strength and control leads to motor incapacitation and the full-time use of a wheelchair by the late teens or early twenties. Many require surgery for their scoliosis. There are currently no treatments or cures.

The Friedreich's Ataxia Research Alliance (FARA) is supporting research that will improve the quality and length of life for those diagnosed with

Friedreich's ataxia and will lead to treatments that eliminate its symptoms.

FARA-supported research and scientific conferences provide hope and accelerate research leading to treatments or cures for people diagnosed with Friedreich's ataxia and for those coping with related neuro-muscular disorders.

In 1996, an international group of scientists — with cooperation and support from patients, patient families, and their physicians — identified the FRDA gene. The gene carries the instructions for making a protein — the protein was named after the disorder and is called frataxin.

FARA was founded in 1998 by its President, Ron Bartek, and his wife, Raychel, to forge a research alliance that would achieve treatments and a cure for Friedreich's ataxia. The Bartek's son, Keith, who is now 22, was diagnosed at age 11, with Friedreich's ataxia — he is in a wheelchair full-time

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Donor Profile, CONTINUED

Wahlestedt's research. In addition to funding the Scripps Research study, Hollin's foundation, which has subsequently merged with the National Fragile X Foundation (NFXF) to give it even more muscle, hosted a Fragile X research conference in Palm Beach for scientists from around the world. This event will be repeated next year.

Thanks largely to Scripps Florida's sophisticated technology and the staff's expertise, the research was performed quickly. And these early promising

results along with the synergy of the research conference have helped the Institute get a piece of a much larger \$21 million federal grant to keep scientists headed in the right direction toward the eventual goal of a drug company developing a medication for fragile X.

The FMR4 discovery highlights the mission of The Translational Research Institute at Scripps Florida, which is focused on translating basic research like the discovery of FMR4 into potential new therapeutics. The Translational Research Institute has a structure similar to a drug discovery

company, and many of the researchers have pharmaceutical experience.

"I'm a big Scripps Florida fan. I've been very pleased with the results of the research, as well as the people we work with at Scripps Florida and our relationship. Claes has been extremely competent and personable," said Hollin.

Besides being a director of CFX/NFXF (the new local entity), Hollin proudly serves as Chairman of the Research Application Sub-committee for the President's Committee for People with Intellectual Disabilities.

and cannot stand up, had a horrific scoliosis surgery, experiences challenges in his hearing and speech, and has a heart condition and diabetes.

To help Keith and others with the disease, the alliance was created and includes research scientists around the world. The alliance has gained momentum over the years. Today it is engaged in a full-court press—to slow, stop, and reverse the damage done by Friedreich's ataxia.

“Although we have no treatment or cure, we have growing hope and knowledge of this disease, along with the confidence that, with everybody working together, we will develop treatments and a cure in the near term”

— Ron Bartek

“Very promising clinical trials are now underway,” said Bartek, “Hopefully, Keith and many other patients will be participating.”

One of FARA's most promising biomedical research grants is at Scripps Research, under the direction of Dr. Joel Gottesfeld, who is considered one of the key investigators involved in FRDA research.

“Joel's work holds tremendous promise of real therapeutic benefit for Friedreich's ataxia patients,” said Ron. “His research is our only hope in the near to mid-term for working with the genetics of the disease. The latest grant that FARA has provided him is by far the largest grant we have ever provided to an academic investigator.”

Joel first got involved in FRDA research by reviewing an article and taking it upon himself and colleagues in his laboratory to meet the challenge of finding a small molecule that could be developed into a pharmaceutical to fix the gene mutation responsible for the disease.

“Raychel and I will never forget an e-mail we received from Joel, who we didn't know at the time,” said Bartek.

“He had obtained DNA samples from several patients that Raychel had organized at a local blood draw, and the results of his initial work showed some hope for therapeutics. We matched up the numbers of the therapeutic samples and one of them happened to be Keith's—two others were from our other sons. It didn't take long for us to fly out to La Jolla and start a most powerful and meaningful relationship with Joel. I still break down telling the story.”

Since that day, Joel's team has developed compounds that reactivate the gene responsible for Friedreich's ataxia, offering hope for an effective treatment for this devastating and often deadly condition.

The class of molecules . . . developed for Friedreich's ataxia may also be useful in Huntington's disease, certain forms of muscular dystrophy, and spinal muscular atrophy . . .

“Joel's research has been wonderfully hopeful, and he's been wildly enthusiastic for the past four years,” said Ron.

“I've met some of the patients and it would be just a dream to be able to help them,” said Joel. “The parents are so thankful for our research and discoveries—it inspires me to do more.”

The molecule that Joel and his colleagues developed for Friedreich's ataxia has been licensed to the biotechnology firm, Repligen, and is currently in preclinical development.

“Our small molecules offer a therapeutic approach to pursue in the near term,” said Joel. “I'm very optimistic.”

Hobe Sound, Florida resident and FARA contributor Peter Crisp is helping to support Dr. Gottesfeld's research through FARA. Peter and his sister are believed to be the oldest living siblings with Friedreich's ataxia.

Peter is 76 and his sister is 79.

“I go to Children's Hospital of Philadelphia whenever Dr. David Lynch asks me to visit.

He and his staff hope that by observing the progression of the disease, further knowledge will be acquired to assist in their research,” said Peter.

“Through FARA and the research at Children's Hospital, I learned about Dr. Gottesfeld's work. I am pleased to provide financial support. Several factors came together leading me to believe that the time was right for me to help. First, I was acquainted with Scripps Research, its work and fine reputation. Second, Dr. Richard Lerner, President of Scripps Research, is a neighbor here in Florida, as is George Conrades, a Scripps Research trustee. Third, Scripps Florida is almost next door to Jupiter Medical Center, which provides clinical services to many Scripps Florida employees. I serve the hospital as Chairman of the Jupiter Medical Center Foundation, which hopes to work closely with Scripps Florida as it grows. Finally, my cordial and informative conversations with Dr. Gottesfeld gave me confidence and comfort that he and his colleagues are committed to excellence in their research efforts.”

The class of molecules that Joel developed for Friedreich's ataxia may also be useful in Huntington's disease, certain forms of muscular dystrophy, and spinal muscular atrophy—the number one genetic killer of children under the age of two, an inherited disease that destroys the nerves controlling voluntary muscle movement, which affects crawling, walking, head and neck control, and even swallowing.

“Taken together, thousands of patients could benefit from this class of molecules,” said Joel.



Peter Crisp

Steve Mayfield:

Globally Impacting Both Medicine and the Environment through Green Algae

> Professor Steve Mayfield is passionate about his work. He specializes in the molecular analysis of gene expression in green algae. His pioneering work on genetically engineered algae to make useful human therapeutic proteins such as antibodies has grown into a biotech company called Rincon Pharmaceuticals.

Algae can be grown at a very large scale at a fraction of the cost of traditional fermentation systems. The algae expression technology that Steve's team uses could facilitate production of any number of human antibodies and other proteins on a massive scale.

Steve has studied algae for the past 25 years (he has been with Scripps Research for 20 of these years). In the late 90's, Scripps Research President Richard A. Lerner, M.D., challenged him to use the algae for the production of therapeutic antibodies. Steve brought this challenge to his lab in 1999 and while starting slow, it has steamrolled ever since. Steve's lab was the first in the world to make antibodies in algae, expressing a human antibody in algae in 2003.

Scripps Research trustee Claudia Skaggs Luttrell and The Skaggs Institute of Chemical Biology here have been integral in advocating for and funding Steve's "out-of-the-box" work.

Recent studies in Steve's lab have demonstrated the production of novel anti-cancer therapeutics that may allow for greatly improved cancer therapy. Steve and his colleagues just finished making an anti-CD19 toxin conjugate that they are using to kill malignant B cells on a B-cell cancer line in cell-based trials. Mice trials will start next. If these animal trials go well, clinical trials will follow. The therapeutic also

might be useful in kidney transplants by eliminating the B-cell that contributes to transplant rejection. Another possible application is multiple sclerosis.



"Realistically, using algae would reduce the cost of making some drugs ten-fold . . . We have the opportunity to globally impact medicine."

— Dr. Steve Mayfield

"We're very excited about this," said Steve. "We're hopeful this will work in the mice trials. No one has ever produced a protein in algae before which can be used on humans."

Algae may offer a cheaper and easier way to produce proteins than current methods. Since algae grow naturally and use carbon dioxide from the air as a carbon source and sunlight as an energy source, whole ponds—tens of thousands of liters—of the algae can be grown once they are modified to produce the protein of interest.

"You can't make a drug if the time and expense is such that you have to sell that drug for hundreds and thousands of dollars," said Steve. "This

has to be the way we make drugs in the future. Realistically, using algae would reduce the cost of making some drugs ten-fold. We have the opportunity to globally impact medicine."

"This is a fast, new, effective way to make a new class of human therapeutic proteins," he said.

Steve has also recognized algae's potential for the production of biofuel molecules, and he is involved with several other San Diego scientists in forming a new research center, the San Diego Center for Sustainable Bioenergy, to tap renewable energy from algae.

High oil prices have sparked a resurgent interest nationwide in alternative fuels, such as ethanol, made by fermenting corn or sugar cane, and biodiesel, made from vegetable oils.

"Microscopic algae are the ultimate crop for producing biodiesel because they grow quickly and with few added

nutrients," said Steve. "We should be putting more resources into algae to address energy needs."

Compared with crops normally used to produce vegetable oil such as soybeans, rapeseed or palm, algae can produce 30 times the amount of oil per acre, according to a Department of Energy report on using algae for fuel.

In comparison, the recent boom in corn-based ethanol production has led to a surge in demand and a doubling of the price of corn over the last year, with ripple effects on other food products.

California's requirement that new power plants supplying the state figure out how to soak up carbon dioxide they

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Awards and Honors

Richard Lerner Receives Research!America Builders of Science Award

Richard A. Lerner, M.D., president of The Scripps Research Institute in La Jolla, California, has been named Research!America's 2008 *Builders of Science* award recipient. He accepted the award at Research!America's 12th Annual Advocacy Awards Gala on March 18 at the Andrew W. Mellon Auditorium in Washington, DC.

Lerner has served as president of Scripps Research since 1986, and today, it is one of the largest private non-profit research organizations in the nation. Its sister institute opened in Jupiter, Florida, in 2004. Lerner also is known as one of the world's experts in the field of catalytic antibodies, which is based on understanding the binding energy of proteins and how that energy can be used to facilitate chemical transformations. His scientific research helped lead to the discovery that ozone, a metabolic product of inflammation, may play a role in atherosclerosis and Alzheimer's disease.

In addition to directing the institute's scientific activities, Lerner is



Scripps Research
President
Dr. Richard A. Lerner

the Lita Annenberg Hazen Professor of Immunochemistry, the Cecil H. and Ida M. Green Chair in Chemistry, and a member of The Skaggs Institute of Chemical Biology at Scripps Research.

Lerner has received numerous prizes and awards, including the Wolfe Prize in Chemistry in 1994, the California Scientist of the Year Award in 1996, and the Paul Ehrlich and Ludwig Darmstaedter Prize in 2003. He is on the editorial boards of several research journals and has been elected to many prestigious scientific societies, boards and academies, including the Royal Swedish Academy of Sciences and the National Academy of Science.

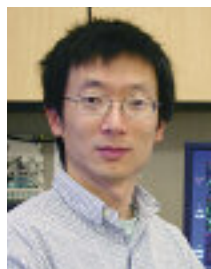
Recipients of Research!America's Advocacy Awards are leading advocates for medical, health and scientific research. The University of Texas Southwestern Medical Center's Donald W. Seldin, M.D., Michael Brown, M.D., and Joseph Goldstein, M.D., were previously recognized with Research!America's Builders of Science Award. Both Brown and Goldstein are Nobel Laureates.

The other recipients of Research!America's 2008 Advocacy Awards are U.S. Senator Edward M. Kennedy; California Governor Arnold Schwarzenegger; amfAR, The Foundation for AIDS Research; William H. Foege, M.D., M.P.H., former Centers for Disease Control and Prevention director, senior fellow, Bill & Melinda Gates Foundation, and emeritus presidential distinguished professor, Emory University Rollins School of Public Health; and Pat Furlong, Parent Project Muscular Dystrophy founding president and chief executive officer.

Research!America is the nation's largest not-for-profit public education and advocacy alliance working to make research to improve health a higher national priority. Its advocacy awards program was established in 1996 to honor outstanding advocates for research. For more information, visit www.researchamerica.org/outreach/awards.html.

Sheng Ding, Kristin Baldwin Win Stem Cell New Faculty Awards

Associate Professor **Sheng Ding, Ph.D.**, and Assistant Professor **Kristin Baldwin, Ph.D.**, of The Scripps Research Institute have won California Institute for Regenerative Medicine (CIRM) New Faculty Awards. The awards for early career scientists are designed to encourage and foster the next generation of clinical and scientific leaders in stem



Dr. Sheng Ding



Dr. Kristin Baldwin

Scientist Profile, CONTINUED

make starting in 2012 could make the energy industry interested.

Steve and his colleagues are talking with potential partners in the energy industry. He has just opened a greenhouse to grow algae at a greater scale on the Scripps Research campus with bays for his two loves — both the medicinal as well as environmental components of his work.

Continued on next page

Awards and Honors, CONTINUED

New Faculty Awards, CONTINUED

cell research. The New Faculty Awards provide salary and research support for up to five years to create a stable environment for new faculty members to build innovative and robust stem cell research programs in California.

In his lab, Ding is applying arrayed large-scale chemical, cDNA, and siRNA libraries and novel high throughput cellular screens to identify and characterize small molecules and genes that can control stem cell fate in various embryonic and adult stem cell systems. He is also investigating the modulation of specific signaling pathways in development and regeneration.

The Baldwin lab is taking two innovative approaches to generate pluripotent cell lines from neurons. Lab members are using cloning by somatic cell nuclear transfer to generate embryonic stem cell lines and mice from the nuclei of individual neurons. They are also trying to generate cell lines from neurons by developing novel methods. They will use these lines to examine the role of irreversible chromosomal changes in neuronal development and disease. Their work will have important implications for generating appropriate *in vitro* models for neurological disease and for cell replacement therapy.

Enrique Saez Wins American Diabetes Association Award

Assistant Professor **Enrique Saez, Ph.D.**, of The Scripps Research Institute has been awarded a five-year Career Development Award from the American Diabetes Association. According to the association, these premier awards support investigators who are establishing independent research programs and are poised to make significant contributions to diabetes research.

“Our studies may provide insight as to why diabetics are more prone to develop atherosclerosis,” Saez said in an interview with the association. “By understanding how



Dr. Enrique Saez

LXR activity is regulated by glucose and pathogenic forms of cholesterol, we may uncover ways to slow development of cardiovascular disease in diabetic patients.”

Sign up for E-News

Scripps Research has launched, “At the Forefront,” an e-newsletter for philanthropists to the Institute. The monthly update includes:

- Informative inside looks into the most promising developments in basic biomedical science.
- News about the Institute’s initiatives, special projects and new programs.
- Invitations to new website content.
- Updates on specific research projects and their impact on diseases such as stroke and heart disease, cancer, alcoholism and chemical dependency, diabetes, Alzheimer’s disease, arthritis, AIDS, and blindness.
- Unique ways for donors to get involved with and support the Institute.
- Profiles of contributors
- Upcoming events

If you would like to receive the newsletter, please sign up at www.scripps.edu/philanthropy. We thank all donors for their ongoing support.

Lab Notes Series

In order to share the ground-breaking work of its scientists with its donors and friends, Scripps Research has launched a series of intimate lectures by its faculty addressing such topics as Alzheimer’s, cancer, and cardiovascular disease. The lectures take place on the Institute’s picturesque La Jolla campus, and are followed by a question and answer session and reception, so participants have plenty of opportunities to interact with the speakers. The free series is called “Lab Notes: An Inside Look at Scripps Research.” The next lecture, by Steven Mayfield, Ph.D., “What in the World can Algae do for you?” will be held on May 21 from 10:00–11:00 a.m. To RSVP, contact Ginny Deary at (858) 784-9367 or ginnyd@scripps.edu.

Sharing Shares—Advantages of Stock Gifts

The gift of an appreciated asset is a powerful way to support The Scripps Research Institute and may be more favorable than a cash donation, resulting in significant tax savings. Plus it's easy to accomplish. The advantages allow you to:

- Receive an income tax charitable deduction for the full market value of long-term appreciated securities
- Avoid capital gains tax on the appreciated value of the securities – charitable giving may be one of your best defenses against capital gains taxes
- Help support the acceleration of discoveries to save lives

“By giving stock, I received a charitable deduction and didn't have to pay the capital gains tax,” said donor Helen Farschon. “I'm very pleased with my stock gift and I'm delighted that I've been able to make a nice charitable contribution.”

“This is a wonderful way to demonstrate your support of breakthrough discoveries at Scripps Research,” said Wendy Scott Keeney, Vice President of Philanthropy.

If you have questions about non-cash gifts of stocks, bonds, or mutual funds, please contact William Burfitt in Scripps Research's Philanthropy Department at (858) 784-2037 or burfitt@scripps.edu.

Generous Gifts Make Possible Merit Awards for Graduate Students

The Scripps Research Institute Office of Graduate Studies has announced the names of students at the Kellogg School of Science and Technology who have been selected to receive merit-based fellowships for the 2007–2008 academic year.

“Congratulations to the award winners,” says Professor **Jeffery Kelly, Ph.D.**, dean of graduate and postgraduate studies, “and many thanks to the donors of these fellowships. Because of their generosity, we have the opportunity to recognize and support outstanding students of biology and chemistry.”

This year's awards include:

The Bagel (pronounced “ba - jél”) Graduate Student Fellowship, which will be held by Crystal Moran. The Bagel Fellowship was established by an anonymous gift in 2003 to endow funding for a student in his or her first critical year of study.

Fletcher Jones Fellowships, which will be held by Brad Charette and Ashley Pratt. These fellowships are supported by 1993 and 2003 grants from The Fletcher Jones Foundation to

endow graduate scholarships at the Kellogg School. The Fletcher Jones Foundation, established in 1969 by mathematician, businessman, and computer science visionary Fletcher Jones, specializes in grants to private colleges and universities, particularly those in California.

Pfeiffer Foundation Scholarships, which go to Peter Watson, Emily Plummer, and Jonathan Lam. The Gustavus and Louise Pfeiffer Research Foundation makes grants to tax exempt institutions for projects or programs carried out in the United States for advancement of medicine and pharmacy, including scientific research, post-graduate scholarship and

fellowship assistance, and studies in nutrition, blindness, deafness, and other physical disabilities.

A San Diego Foundation scholarship from the Norman & Margaret Lassey Fund, which will be held by Florina Voica. The San Diego Foundation is a community resource for receiving, managing, and distributing charitable funds to support organizations within the San Diego area.

The Delia Baxter Fellowship, which will be held by Erin Anderson, and the Donald Baxter Fellowship, which will be held by Miller Tran. The Donald and Delia Baxter Foundation was established to advance charitable, scientific, and educational purposes, primarily at medical and scientific schools of higher learning in California.

The selection criteria for these fellowships are primarily based on excellence in research as demonstrated by publications and contributions to the graduate program.



Graduate Students:
Top Row Standing: Crystal Moran, Emily Plummer, Peter Watson, Florina Voica, Ashley Pratt, Brad Charette
Bottom Row Sitting: Jonathan Lam, Erin Anderson, Miller Tran

The Scripps Council of 100

> The Scripps Council of 100 consists of individuals, couples, and representatives of corporations or foundations that contribute \$100,000 annually or make a single contribution of \$1 million or more to The Scripps Research Institute.

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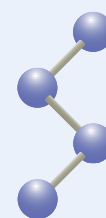
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