INSTITUTE UPDATE

Renowned Researcher Jeanne Loring Heads New Stem Cell Center at Scripps Research

> Professor Jeanne Loring has been named founding director of the newly created Center for Regenerative Medicine at The Scripps Research Institute in La Jolla, California.

Loring is an internationally recognized authority in the emerging field of stem cell research, which explores the potential of these cells to differentiate into various cell types that may be used to treat diseases and conditions such as Parkinson's and Alzheimer's, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.

“The potential of stem cell research is vast,” said Scripps Research President Richard A. Lerner, M.D., in announcing the creation of the new center. “It takes a scientist of Professor Loring's foresight, knowledge, and experience in basic and applied research to lead the institute's team to new discoveries that will significantly benefit human health.”

“I am excited about the potential of this new center to push research in the field forward,” said Loring. “I'm looking forward to growing the center in the Scripps Research traditions of cross-disciplinary collaboration and cutting-edge science.”

Researchers at the Scripps Research Center for Regenerative Medicine will explore many aspects of stem cells, including embryonic, continued on page 2

RESEARCH UPDATE

Scientists Identify Potential New Target for Treating Metastatic Cancer

> A team of scientists at The Scripps Research Institute have identified a human protein that may be a new target for future cancer therapies.

By experimentally blocking the action of this protein, called CD151, the team showed they could stop cancer cells from metastasizing, or spreading from one tumor to establish new tumors elsewhere.

Metastasis is a hallmark of late-stage cancer and contributes significantly to the large number of cancer deaths each year in the United States. Scripps Research Professor James Quigley and his colleagues described how blocking CD151 stopped the spread of human cancer cells within fertilized chicken embryos—an experimental model used for studying cancer metastasis. continued on page 2
Jeanne Loring, CONTINUED

adult, and malignant cancer stem cells, from their basic biology to potential clinical applications in drug discovery, drug delivery, and cell therapy.

The new center’s major mission is to provide infrastructure to support collaboration and strategic partnerships in human stem cell research and train the next generation of stem cell scientists.

An intensive NIH-sponsored human embryonic stem cell laboratory course will be offered this fall, and the center will be the site of the San Diego area training course supported by the California Institute for Regenerative Medicine.

Loring has a B.S. in Molecular Biology from the University of Washington and a Ph.D. in Developmental Neurobiology from the University of Oregon. She served on the faculty of the University of California, Davis, and has held research and management positions at biotechnology companies including Hana Biologics, GenPharm International, Molecular Dynamics, and Incyte Genomics, and was founder and chief scientific officer of Arcos BioScience (now part of Novocell). She joined the faculty of the Burnham Institute for Medical Research as a principal investigator in January 2004 and was one of the principal architects of Burnham’s successful human embryonic stem cell program. She joined The Scripps Research Institute last October.

Cancer, CONTINUED

“Targeting this protein keeps the cancer cells tied to their tumors,” says Quigley. “This may be the first time anyone has shown a potential way of blocking cancer metastasis at its very earliest stage—as the cells are first pulling away from their tumors of origin.”

While these results provide only a proof of concept, they suggest it may be possible to design new ways of fighting cancer by treating people with drugs that block CD151.

Any new cancer treatments based on this discovery would likely take years to develop and would have to prove effective in numerous preclinical experiments and in human safety and efficacy trials before finding their way into the clinic.

The need for more effective cancer treatments is profound. More than half a million people a year die from cancer in the United States alone, making it the second-leading cause of death in this country.

Caused by DNA mutations within a cell that disrupts its programming and cause it to begin dividing, cancer can be pernicious. Over time, one cell on a tissue within the body can grow into a large cluster of cells, forming a tumor that may severely interfere with the function of that tissue. Doctors can remove tumors by treating them with drugs, bombarding them with radiation, or excising them surgically, but these treatments often fail, ultimately because the tumor cells don’t stay put. Instead they metastasize—separating from the primary tumor and establishing a new focus of cancer cells elsewhere in the body.

When cancer cells metastasize, they must accomplish a sequential series of feats in order to successfully establish new tumors. First, they have to break free, enter the bloodstream, survive in the circulation, come to a halt somewhere else in the body, invade a new tissue, establish a new tumor, and find a way of supplying themselves with blood and nutrients as they divide and grow into a new colony.

Cancer researchers have long focused on the fact that as cancer cells make this journey, they interact with a changing environment by altering the expression of their genes and changing the assortment of proteins on their surfaces.

Interfering with these proteins is a proven way of blocking metastasis, but much of the research to date has focused on targeting those proteins involved in the later stages of the metastatic journey—the ones that help the cells enter the bloodstream, migrate, or form new blood supply lines to feed a growing tumor, for instance. Researchers have never found a way to target a protein and block a tumor cell from detaching in the first place.

Now, Quigley and his colleagues have shown for the first time that they can block tumor cell detachment and halt metastasis by targeting CD151.

The work started several years ago, when Quigley and his colleagues generated a unique antibody in mice that blocked metastasis. The antibody, as it turned out, targets CD151, a protein that sits in the cell membrane and had been associated with cell motility—the ability of cells to crawl. So, Quigley and his colleagues initially assumed that the antibody would stop metastasis by preventing cancer cells from crawling. They were surprised to discover how it actually worked.

The scientists used an experimental system with fertilized chicken embryos with no shells. These embryos develop blood vessels when left in an incubator for several days, and cancer cells from metastatic tumors implanted into them will readily migrate through these blood vessels to form new tumor colonies in under a week. When Quigley and his colleagues treated the embryos with the antibodies, however, they found that the tumors did not metastasize. Instead, the cancer cells stayed tightly clustered.

It turns out that the antibody does not block motility at all. It halts "intravasation”—the moment when a cancer cell breaks free from its tumor. Somehow the antibody prevents the interaction that allows the cell to release itself. Under the microscope, these cells can be seen in real time, trying to crawl away from the tumor mass only to snap back every time. The cells can crawl perfectly, but they are tied to their tumor.

The exact mechanism of this tethering is unclear, but the principle is clear enough. Without the antibodies, the cancer cells rapidly escape into the embryo vasculature and establish new tumors elsewhere.
Scripps Florida Awarded $7.6 Million Grant to Develop Novel Treatment for Parkinson’s Disease

> The National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH), has awarded a $7.6 million multi-year grant to Scripps Florida, a division of The Scripps Research Institute, to develop the next generation of medication to treat Parkinson’s disease.

Philip LoGrasso, associate professor and senior director for drug discovery at Scripps Florida, will lead the project as principal investigator. LoGrasso, who joined Scripps Florida in 2005, previously held positions at Merck and the NIH.

The new five-year grant will fund research to develop a compound to treat neurodegeneration in Parkinson’s disease. The goal of the project is to bring the potential treatment to the point where Scripps Research and potential partners can file an application for an investigational new drug—the first step in the lengthy clinical trials process required by the U.S. Food and Drug Administration.

An estimated one million Americans are believed to suffer from Parkinson’s disease, according to the Parkinson’s Disease Foundation; approximately 40,000 new cases are reported annually. Patients with Parkinson’s suffer from a loss of dopaminergic neurons, the source of dopamine, a neurotransmitter that plays a key role in motor reflexes and cognition. While some loss of dopaminergic neurons is common, Parkinson’s patients routinely lose more than half.

“Development of a drug that prevents dopaminergic neurodegeneration would be a quantum leap in the clinical treatment of Parkinson’s disease.”
—Dr. Philip LoGrasso

To develop the new small-molecule compound, LoGrasso will work with a team of Scripps Research scientists. Together, the team represents a range of experience in pharmaceutical preclinical drug development, encompassing the fields of medicinal chemistry, biochemistry, cell biology, structural biology, behavioral pharmacology, drug metabolism and pharmacokinetics, and toxicology.

The team will use what LoGrasso calls a classical pharmaceutical approach to drug development, which involves annual milestones and multiple compound tracking.

“Our research plan is designed to mitigate the risk of developing a single compound that may fail due to specific problems, and to maximize the chance for clinical success by having back-up compounds,” LoGrasso said. “We believe that using this approach to optimize small-molecule inhibitors will create a series of compounds with favorable pharmacokinetic properties and safety profiles.”

The scientists will examine small-molecule compounds that inhibit c-jun-N-terminal kinase 2/3 (JNK 2/3). Pronounced Junk, JNK 2/3 is an important contributor to stress-induced apoptosis (cell death) and has been shown to play a significant role in neuronal survival. As such, the kinase is a highly viable target for drugs to treat neurodegenerative disorders like Parkinson’s disease.

Previous research has shown that small-molecule and peptide inhibitors of the JNK target protect dopaminergic neurons in both acute and chronic models of Parkinson’s disease. Previous research has also shown that the JNK2/3 knockout mouse models—mice that lack the gene for JNK2/3—suffer fewer Parkinson’s-like symptoms.

“The scientists hope to identify approximately three compounds that demonstrate in vivo efficacy by the third year, and a top compound by year four of the research program.

“When we’re finished, our aim it is to have a safe, efficacious compound with sufficient preclinical safety data to support human clinical studies,” LoGrasso said.
Dan Salomon – A Quest to Improve and Extend the Lives of Kidney, Liver and Islet Transplant Patients

> Using the explosion of knowledge made available from the human genome project, Scripps Research associate professor Daniel Salomon, M.D.’s research is focused on using the latest technologies to advance the genomics, proteomics, and genetics of kidney, liver, and islet transplantation.

Transplantation of organs such as kidneys, livers, hearts and lungs save thousands of lives each year. Dan’s studies involve patients with kidney, liver and islet transplants and diseases such as kidney failure, diabetes, hepatitis, and cancer.

“The main objective of our lab is to advance our understanding of cell and organ transplantation in ways that will yield direct benefit to patients with diabetes mellitus, kidney and liver transplants,” said Dan.

Dan and his colleagues have been monitoring several hundred patients who have had kidney and liver transplant surgeries with technologies for gene expression profiling and proteomics, and several thousand transplant patients by complex trait genetics.

One of his goals is to answer one of the most pressing problems in kidney transplantation: why do some patients do well after a transplant and others do not?

“Fifty percent of transplant patients lose their kidneys within ten to twelve years,” said Dan. “We’re studying some 2,400 patients with kidney transplants, and are looking at the genetic basis and control of why some patients do well and others have problems.”

In both organ and cell transplants, there is a danger of both infection and transplant rejection, arising from the fact that a donated organ or cell is foreign to the transplant patient’s body. Left alone, the person’s immune system will detect the foreign tissue and mount an immune response, killing the new tissue, and leaving the patient no better off than before the transplant. Wishing to avoid transplant rejection, doctors treat patients who have had transplantation with a powerful class of drugs, known as immunosuppressants, which weaken the immune response and mitigate the danger. With adequate doses of immunosuppressant drugs, a transplanted organ can survive and function well for decades. However, these drugs make transplant patients more likely to suffer heart disease, diabetes, infection and cancer, and can slowly poison the very kidney they are protecting in kidney transplants or lead to liver transplant patients requiring a kidney transplant after five to ten years.

Because of all the drug toxicities, one of the major challenges in treatment following transplant surgery is to determine the proper regimen of drugs needed for a patient.

Patients must be given a strong enough dose of drugs so that their immune systems are kept in check. At the same time, they cannot receive so high a dose that the drugs are too toxic. Only with the right balance is successful transplantation achieved and the many risks minimized.

“Unfortunately the reality,” says Dan, “is that there is no metric, no blood test, for adequate or safe immunosuppression. As a consequence, doctors are forced to determine immunosuppressive drug doses and combinations based on only published results from large trials and their clinical judgment and experience. This is a critical aspect of medicine but we have learned the tremendous value of objective tests that can identify the individual nature of each patient and their response to a drug or a drug combination.”

Dan would like to change that and is hopeful that he can within the next couple of years. He is using the discoveries of genomic science to build a new set of tools so that doctors can measure and predict with a blood test how a patient will respond to immunosuppressive drugs. With such tools, transplant doctors could monitor patients regularly to make sure their treatment is always optimal and maximally safe.

There are two central theories being tested in Dan’s work. The first theory is that there is a genetic “signature” within donors and recipients that predict the best course of treatment following a transplant surgery. This first signature is fixed by our genetic inheritance and the choice of a particular donor for a recipient. The second theory is that there is a genomic signature in the blood that at any given moment reflects the level of immunosuppression and the status of the immune response to the transplanted
cells or organ. The genomic signature in blood is constantly changing and reflects the dynamics of health and disease. Dan is working on understanding both signatures and developing ways to detect it within the laboratory. He has made progress, showing for the first time that one can diagnose acute rejection and chronic rejection by profiling gene and protein expression in the peripheral blood using high density DNA microarrays and tandem mass spectrometry proteomics.

“We’re applying multiple new technologies to understanding how to diagnose, manage patients, and improve the safety of therapies to organ and cell transplantation,” said Dan. “In all our work, the objective is to work in a multi-dimensional genomic space created by an ongoing and iterative integration of the latest technologies with cell-based preclinical animal models and human clinical studies.”

One unique feature of Dan’s research is that all the genetics are done on both the patients and their kidney donors.

“The genetics of the patient receiving the kidney determines the character of the immune response, but it’s the genetics of the donor that determines the impact of the transplantation,” said Dan. “What we’re hoping to come out with is an understanding of what makes a good donor and what is it about the donor organ that determines the long-term outcome of the transplant.”

Dan is particularly appreciative of the many new technologies and collaborations available at Scripps Research. “We have powerful cutting-edge technologies for genomics, proteomics, animal model building, cell biology and small molecule discovery which speed research,” he said. “My research is constantly drawing on these resources.”

One of Dan’s patients is Mark Baber, an ex-Microsoft executive originally from the Seattle area. After Mark and his wife Molly, a successful AT&T executive, moved to San Diego, Dan took over care of Mark’s kidney transplant that he received just before moving because he is a diabetic. Mark and Molly struck up a friendship with Dan and learned about his research. Before Molly’s sudden and tragic death from a cerebral aneurysm, she and Dan were working on a fund to support research in his laboratory on transplantation and diabetes. In her memory, Mark created the Molly Baber Research Fund for Diabetes and Transplantation Medicine.

“In lieu of flowers, I asked people to contribute to the fund at the memorial service,” said Mark. “I knew it was something that Molly would have wanted to have done.”

Mark has done a couple of fundraisers recently for Dan’s research and has now forged a relationship with the William Church Winery of Woodinville, Washington, in which the winery is donating $1.00 for every bottle of their new cabernet sold to the Molly Baber Research Fund.

“I think this is a remarkable gesture to support medical research here,” said Dan. “It was my pleasure to know Molly and experience her incredible sense of life and unselfish commitment to helping people. In creating this research fund, we are honoring her spirit and dedicating our research to her passions for health, scientific and human understanding, integrity and excellence.”

“When you’re a diabetic since age 11, you have a long exposure to different doctors,” said Mark. “What I’ve noticed about Dan is that he is not only an incredibly talented and gifted physician and researcher, but he has the unique ability to talk to a patient in almost a peer-to-peer way. His sensitivity stands out.”

Dan has also earned the admiration of his colleagues. “Dr. Salomon is a great mentor and an amazing person,” said Staff Scientist Stephanie Cherqui, Ph.D., who works in Dan’s lab.

Dan was formerly the Medical Director of the Kidney and Heart Transplant Programs at the University of Florida. He later moved to the National Institutes of Health (NIH). He came to Scripps Research in 1993.

“I had visited a collaborator from Scripps Research while I worked at the NIH,” said Dan. “I liked the focus of basic science and how people were really driven to work collaboratively here. I saw the tremendous potential of working in such a science-based environment to create translational research, moving basic discoveries from the bench to the bedside where they can help people live healthier and more productive lives.”

Dan was a chemistry major at Northwestern University, received his M.D. from Stritch–Loyola School of Medicine in Chicago, trained at Cedars–Sinai/UCLA for internal medicine and did his postdoctoral work in transplantation and immunology at Harvard Medical School. While he modestly shakes off his many honors, there is a recent one that he is particularly proud of – being inducted into the Alpha Omega Alpha Society, a medical honorary society which is the equivalent of Phi Beta Kappa, by the Stritch–Loyola School of Medicine.

“The school had tracked my work,” said Dan. “They were impressed with both the basic bench research and the translation to bedside that it entailed. I was invited and gave several lectures on campus and addressed the graduating class. It was a wonderful honor and very meaningful to me, and it was great to be given the opportunity to stir and challenge the young minds of future physicians and scientists.”
Awards and Honors

Accolades Abound in Scripps Research Internship Programs

> Scripps Research internship programs for high school students have produced many success stories.

In Florida, Seminole Ridge Community High School senior Lucas Ortiz, who interned last year in the Busby lab, took first place in the biochemistry division at the Palm Beach County Science and Engineering Fair. He then went on to capture the Jane C. Hart Award of Excellence that designated his as the “top project overall” at the fair. Ortiz’s other honors include being named South Florida Science Museum 2008 Student of the Year.

At the Greater San Diego Science and Engineering Fair, three interns from last summer’s program won first prize awards:

• Mr. Miguel High School senior Laika Roy, who interned in the Vogt lab with mentor Research Associate Marco Gymnopoulou;
• Mr. Miguel High School senior Adella Fejeran, who interned in the Potter/Carragher lab with mentor Research Technician Teddy Ajero, Jr.; and
• Theresa Tran, who interned in the Kuhn lab with mentor Ph.D. candidate Dena Marrinucci. In addition to her first prize award, Tran also captured the overall Grand Prize in the Senior Division and was hired to continue to work part-time in the Kuhn lab.

“I’ve had the opportunity to mentor two high school students here at Scripps Research,” says Marrinucci. “Each experience was phenomenal and I have watched both interns learn a great deal in a very short period of time while learning so much myself.

These interns became integral lab members and contributed to ongoing transdisciplinary research.

Theresa winning first prize in the science fair this year was just the icing on the cake and we are all just so proud of all the great work she did.”

The Scripps Research Institute’s Gerald Dodson, a research associate in the Russell lab, and Michelle Duquette-Huber, a research associate in the McGowan lab, have won Ruth L. Kirschstein National Research Service Awards.

According to the NIH, the purpose of the award “is to help ensure that highly trained physician/scientists will be available in adequate numbers and in the appropriate research areas and fields to meet the nation’s mental health, drug abuse and addiction, alcohol abuse and alcoholism, and environmental health sciences research needs.”

Gerald Dodson and Michelle Duquette-Huber Win NIH Awards

Research intern Theresa Tran (left) and mentor Ph.D. candidate Dena Marrinucci of the Kuhn lab pose in front of Tran’s Grand Prize-winning poster at the Greater San Diego Science and Engineering Fair.

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Friendship, Laughter and Fundraising

And now you can harness the power of friendship to advance some of today’s most promising research...form a giving circle to support Scripps Research.

Giving circles are the new wave of grass-roots philanthropy—increasing the power of individual gifts by pooling donations. And perhaps the most compelling reason to start a giving circle is that they are a way to connect you with people who are passionate about helping find tomorrow’s medical breakthroughs.

Start with a simple dinner—gather your friends, enjoy good food and then talk about diseases that have affected you or someone in your circle. It will give you a chance to support one another and then turn that support into action.

With a small contribution from each member, you can make a huge difference in cancer research, help us find answers for degenerative diseases like Alzheimer’s and Parkinson’s, or ensure healthier futures for our children and grandchildren.

And this kind of grass-roots fundraising works! An article in USA Today talks about a group called Dining for Women that started in 2003 with 20 women in Greenville, S.C. They decided to meet once a month for a pot-luck dinner, pool the money they would have spent in a restaurant and give it to a non-profit organization. They raised $700 at the first meeting and, by 2005, they had formed a non-profit organization.

Dining for Women now has more than 90 chapters with about 2,200 members nationwide that raise $13,000 to $15,000 each month—all of which is donated to one organization designated for that month.

While most giving circles won’t grow beyond a single living room or local restaurant, it’s the collective strength of the group that makes them so powerful.

The possibilities are limitless when you bring together people who share your commitment to Scripps Research.

For more information, please contact Jessica Yingling, Ph.D., (858) 784-2874 or jyingling@scripps.edu.

A Bequest to Fight Disease—A Life Long Gift

When you have done all you can to provide for your family, you can give no better gift for future generations than progress in the prevention, improved treatments, or cures for people diagnosed with devastating diseases.

Bequests form a major part of our income, and much of our work could not continue if it were not for people choosing to remember us in their wills or trusts.

No matter how small or large the financial gift, property, or asset you choose to leave to The Scripps Research Institute, it is greatly appreciated. All bequest income is invested prudently to recognize the achievement of a lifetime’s saving.

If you choose to make an investment in the advancement of biological science with a bequest to The Scripps Research Institute, please let us know so we can thank you personally. Too often, we only hear of a donor’s generosity and thoughtfulness after their passing. We would very much appreciate the opportunity to show our gratitude during your lifetime.

Whatever you choose to do, your gift will make a difference.

You can also indicate if you would like your bequest to be directed towards research into a specific disease or to our graduate program.

If you would like more information about The Scripps Research Institute, or you are considering a gift in your will or trust to The Scripps Research Institute, please contact, Cheryl H. Dean, Esq., Planned Giving Counsel, (858) 784-2380 or email cdean@scripps.edu.
Partners

1. Scripps Research continued its Frontiers in Science lecture series for donors and friends in March at the Estancia La Jolla Hotel and Spa. The lecture focused on Scripps Research’s nationally ranked graduate school, The Kellogg School of Science and Technology, which provides world-class training in the life sciences. Stephen Mayfield, Ph.D., and Jamie Williamson, Ph.D., two of the graduate school deans spoke about the school at the event. Graduate students Joie Garfunkle and Andrew Webb also spoke about their research. Pictured at the reception are long-time supporter Ron Newell and graduate student Joie Garfunkle.

2. Friends of Scripps Florida gathered for a “sneak peak” of the permanent campus during a series of hard-hat tours offered throughout March and April (photo at bottom left). Guests were presented a showcase of the Advanced Technologies building which also houses Scripps Florida’s education pavilion, long-distance learning library, and conference center. Campus construction will be complete by Fall 2008. A dedication is scheduled for February 2009.

3. George Elmore, a major philanthropist to Scripps Research, enjoyed a presentation made by Deborah Leach-Scampavia, Scripps Florida’s science education outreach administrator, during a recent tour of the campus construction site.

4. This Spring, James and Dorothy Patterson opened up their oceanfront Palm Beach home to host a cocktail reception and buffet supper in honor of Scripps Florida, which was highlighted by a featured performance by renowned Russian piano virtuoso, Andrei Gavrilov. Joining the Pattersons in hosting the evening were Dr. and Mrs. John Whelton, and Dr. and Mrs. Charles Weissmann. Dr. Weissmann is Professor and Chairman of the Department of Infectology at Scripps Florida. Guests were welcomed by Dr. Weissmann and Dr. Richard A. Lerner, president of The Scripps Research Institute, who shared a number of the astounding research discoveries coming out of Scripps Florida. Institute trustee Alex Dreyfoos, spoke to guests, as well, of the incredible benefit that the Institute has contributed economically, educationally and on a global scale for Florida. Pictured here are James and Dorothy Patterson with Dr. Richard Lerner.

Contact Us: For more information about Scripps Research, visit our web page at www.scripps.edu/philanthropy

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