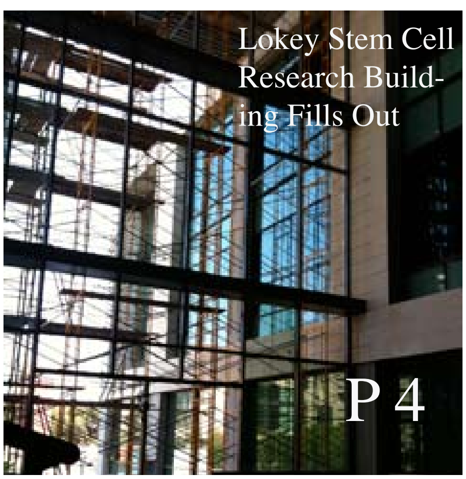
STANFORD
MEDICINE
Institute for Stem Cell Biology & Regenerative Medicine

DEC 2009



Irving Weissman Assumes Presidency of ISSCR

In July, institute director Irv Weissman, MD became the seventh president of the International Society for Stem Cell Research (ISSCR). Dr. Weissman begins his year as president of the society with a broad set of goals aimed at promoting stem cell research, pushing along the process to turn research into cures, and protecting the public from unproven therapies. Among the goals he is promoting are:

• Listing unproven therapies: Weissman wants to create a list of unproven therapies, like the American Cancer Society does for cancer treatments. Currently, a large number of people spend a great deal of money to seeing or undergoing stem cell treatments in foreign countries. Many of these treatments are scientifically

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unproven, but there is currently no clearing house for reliable information about what stem cell treatments are worthwhile and which are not.

• Enlarging the big tent: The ISSCR is an international society, but currently holds only one international meeting per year. Weissman wants to have more regional meetings around the world. These meetings would provide a forum for additional discussions among world leaders in science and government.

• Clean up the language: Weissman has noted that people now call many things a "stem cell treatment," although what is often being used is not purified stem cells, but bone marrow or blood products. What is and is not a stem cell therapy should be defined.

•Improving graduate programs: Weissman wants provide guidance and advice to graduate programs in stem cell science by making the ISSCR a clearning house for information about best practices in the field. Stem cell research is its own field, with requirements and approaches that are different from other fields like developmental biology.

hESC Classes in iPS Cell Techniques

The Center for Human Embryonic Stem Cell Research and Education (hESC) holds occasional, multi-day training classes in induced pluripotent stem cell technology and techniques. The course includes detailed lectures and practical protocols for deriving iPS cells, although there will be no hands on laboratory instruction. The class are free of charge and open to researchers associated with CIRM-funded institutions.

If you sign up at the link below, you will be notified when a new class is scheduled.

Apply at:
http://hesc.stanford.edu/education/apply.html

Researchers get $51.7 million in state grants to develop stem-cell based therapies

BY KRISTA CONGER

Three teams headed by researchers at the Stanford University School of Medicine today received $51.7 million from the California Institute for Regenerative Medicine to develop FDA-approved therapies within the next four years for acute myeloid leukemia, the lethal skin-blistering disease epidermolysis bullosa and ischemic stroke. It is the largest amount Stanford has received in a single round of funding from CIRM.

The teams are headed by Irving Weissman, MD; Alfred Lane, MD; and Gary Steinberg, MD, PhD, respectively.

The Stanford grants were part of a total of $250 million awarded today by CIRM's 29-member governing board to 14 multidisciplinary teams in California, Canada and the United Kingdom. This is the agency's largest funding round since its inception.

The Disease Team research awards are designed to quickly bring promising therapies to patients through teams that include basic scientists, clinicians and industry. CIRM President Alan Trounson, PhD, said in a statement that the pace of the Disease Team projects stands in contrast to the decade or more that's usually required to reach clinical trials. "Scientists have talked for years about the need to find ways to speed the pace of discovery," he said. "By encouraging applicants to form teams composed of the best researchers from around the world, we think CIRM will set a new standard for how translational research should be funded."

"We are gratified that CIRM has funded our application to develop an antibody therapy for human acute myeloid leukemia," said Weissman, whose team will receive $20 million over the next four years. He is the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. "The funding will help us advance our preclinical finding that the AML cancer stem cells express a 'don't eat me' signal called CD47 that protects them from the immune system. Blocking this signal with an antibody results in the elimination of these cells and is a promising avenue to human therapy."

Together with Weissman, co-principal investigators Ravindra Majeti, MD, PhD, assistant professor of hematology, and Beverly Mitchell, MD, director of Stanford's Cancer Center, will collaborate with partners in the United Kingdom to conduct coordinated basic research, clinical studies and the development of pre-clinical therapeutics leading to a phase-1 clinical trial of a stem cell-targeted antibody therapy for the disease. Weissman and Majeti are also members of Stanford's Cancer Center.

Lane, professor and chair of dermatology, heads a team that will receive $11.7 million to use stem cell therapy to treat a devastating genetic skin condition called epidermolysis bullosa, or EB. People with a version of the condition called dominant dystrophic EB suffer severe blistering and sloughing of the skin that is usually lethal by young adulthood. The team will use patient-specific induced pluripotent stem, or iPS, cells to correct the genetic defect that causes the disease.

"The Stanford group has been working on EB for the past 15 or 16 years, and this is a very exciting next iteration of our work" said co-principal investigator Anthony Oro, MD, an associate professor of dermatology specializing in skin differentiation and development. "We feel that we're ready to take the treatment of this disease to the next step. We have an amazing group of people working on this disease." The international group includes Stanford stem cell expert and co-principal investigator Marius Wernig, MD, as well as Paul Khavari, MD, PhD; Peter Marinkovich, MD; Howard Chang, MD, PhD; and Seung Kim, MD. Khavari, Marinkovich, Chang and Kim are also members of Stanford's Cancer Center.

Stinehart Reed Awards Announced

The Institute for Stem Cell Biology and Regenerative Medicine at Stanford is pleased to announce the recipients of the first Stinehart Reed Seed Grants for Stem Cell Research. These awards are made possible by the generous gift of William Stinehart, Jr. and the Reed Foundation. They are designed to support developing programs in stem cell research that have significant potential for impact but are not receiving external funding. We received over 40 high quality, interesting and innovative applications. Many proposals received very high scores, making it difficult for the reviewers to select the top five for funding. Congratulations to all who applied for their excellent proposals and particular congratulations to this year's Stinehart Reed Award recipients listed below!

Michael Longaker: Identification and Characterization of Skeletal Progenitors

Ravi Majeti: Molecular Evolution of Acute Myeloid Leukemia Stem Cell Genomes

Roel Nusse: Investigating a transcriptional regulator of niche-stem cell signaling

Tom Rando: Molecular Regulation of Stem Cell Quiescence and Activation

Marius Wernig: Direct Generation of Functional Neurons from Fibroblasts by Defined Factors

Center for Human Embryonic Stem Cell Research and Education

hESC

NEWS

Scientists turn stem cells into precursors for germ cells

Human embryonic stem cells derived from excess IVF embryos may help scientists unlock the mysteries of infertility for other couples struggling to conceive, according to new research from the Stanford University School of Medicine. Researchers at the school have devised a way to efficiently coax the cells to become human germ cells — the precursors of egg and sperm cells — in the laboratory. Unlike previous research, which yielded primarily immature germ cells, the cells in this most-recent study functioned well enough to generate sperm cells.

"Ten to 15 percent of couples are infertile," said senior author and hESC director Renee Reijo Pera, PhD. "About half of these cases are due to an inability to make eggs or sperm. And yet deleting or increasing the expression of genes in the womb to understand why is both impossible and unethical. Figuring out the genetic 'recipe' needed to develop human germ cells in the laboratory will give us the tools we need to trace what's going wrong for these people." Previous efforts to study infertility have been hampered by the fact that — unlike many other biological processes — the human reproductive cycle cannot be adequately studied in animal models. And because germ cells begin to form very early in embryonic development (by eight to 10 weeks), there's been a dearth of human material to work with. "Humans have a unique reproductive system," Reijo Pera said. "Until now we've relied on studies in mice to understand human germ cell differentiation, but the reproductive genes are not the same. This is the first evidence that you can create functional human germ cells in a laboratory."

In this study, the researchers treated human embryonic stem cells with proteins known to stimulate germ cell formation and isolated those that began to express germ-cell-specific genes — about 5 percent of the total. In addition to expressing key genes, these cells also began to remove modifications, or methyl groups, to their DNA that confer cell-specific traits that would interfere with their ability to function as germ cells. Such epigenetic reprogramming is a hallmark of germ cell formation.

They then used a technique called RNA silencing to examine how blocking the expression of each of three genes in the embryonic stem cells affected germ cell development. Conversely, they also investigated what happened when these genes were overexpressed.

They found that one gene, DAZL, functions very early in germ cell development, while two others, DAZ1 and BOULE, stimulate the then-mature germ cells to divide to form gametes. Overexpressing the three proteins together allowed the researchers to generate haploid cells — those with only one copy of each chromosome — expressing proteins found in mature sperm. (When a sperm and an egg join, the resulting fertilized egg again has two copies of each chromosome.) When treated in this manner, about 2 percent of the differentiated human embryonic stem cells were haploid after 14 days of differentiation.

The effect of the DAZ family members on the embryonic stem cells varied according to whether the cells were derived from a male or a female embryo. Over-

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CIRM NEWS

News and Information from the
California Institute for Regenerative Medicine

Stanford researchers get a large chunk of $16 million in CIRM grants

The California state stem cell agency today awarded three Stanford University researchers a total of $4.2 million to investigate what makes stem cells tick. The three-year grants are meant to provide the foundation for achieving clinical advances in the future.

Helen Blau, PhD, the Donald E. and Delia B. Baxter Professor at Stanford's School of Medicine; Julien Sage, PhD, an assistant professor of pediatrics and of genetics at the School of Medicine; and biologist Susan McConnell, PhD, the Susan B. Ford professor, were each awarded about $1.4 million as part of the agency's Basic Biology Awards I grant round. All told, the agency, officially known as the California Institute of Regenerative Medicine, awarded a total of $16.4 million to 12 recipients at five California institutions in this funding cycle.

"These basic biology grants will generate new ideas for future therapies and also provide information to help overcome barriers in bringing therapies to patients," said CIRM president Alan Trounson in a statement from the agency.

Blau, who directs the Baxter Laboratory of Genetic Pharmacology and is an associate member of Stanford's Stem Cell Biology and Regenerative Medicine Institute, received her grant to investigate the molecular basis of how adult cells are reprogrammed to look and act like human embryonic stem cells. Ideally this information could be used to increase the efficiency of creation of these iPS cells. Sage was awarded funds to study the role of the retinoblastoma protein in cellular reprogramming. Both Blau and Sage are members of Stanford's Cancer Center.

McConnell, who is a biology professor in the Stanford School of Humanities and Sciences, received a grant to identify and characterize dopaminergic neurons derived from human embryonic stem cells.

The stem cell agency's 29-member governing board also discussed the recommendations of California's Little Hoover Commission regarding its organizational structure. In addition, it approved two new requests for applications for grants: one focused on stem cell transplantation and immunology, and another aimed at recruiting leading stem cell researchers to California.

In total, Stanford has received $111.3 million in grants from the state's stem cell agency.

CIRM ICOC Meetings:
October 27th-28th
Los Angeles

December 9th-10th
Irvine

Standards and Work Group Meeting:

September 17th-18th
San Francisco

Building for the future: New Home, Faculty

Maximilian Diehn, Rajat Rohagi, and Ravindra Majeti, in front of the Lorry I. Lokey Stem Cell Research Building

The Lorry I. Lokey Stem Cell Research Building is speeding toward completion. Construction is running on-time and on-budget, with building slated to be finished by summer 2010, says facilities coordinator Chris Shay. Researchers and staff are expected to start moving in that fall.

The process has been given a boost by an advanced system in which many pieces of the building are planned, designed and built off-site, then brought to campus for installation. "We are building this building like Boeing builds the 777," Shay says. "The system has dramatically cut the number of corrections we have to make at the job site."

The downturn in the economy and trouble in the building sector generally has also provided an assist. "With so little construction going on in the Bay Area, the contractors have kept on only their best workers, so we have all the A teams working here," Shay says.

The institute has also garnered some exciting new additions to an already impressive corps of researchers. Maximilian Diehn, MD, PhD, is an oncologist who has extensive experience in cancer stem cell research, much of it in association with the laboratory of Michael F. Clarke. Diehn was courted by a number of major universities before accepting an assistant professorship in Stanford's department of radiation oncology. He is a member of the Stem Cell Institute and the Cancer Center. Most recently, Diehn received attention for his research showing why cancer stem cells are resistant to radiation therapy.

Ravindra Mahjeti, MD, PhD, has also received a recent notable success. As a member of the Weissman laboratory, Majeti was first author of a paper reporting that leukemia cells avoid the immune system by displaying the protein CD-47, which the researchers propose acts as a "don't eat me" signal to the body's macrophages. The Stem Cell Institute leadership feels fortunate to get Majeti, who has taken an assistant professorship in the departement of hematology.

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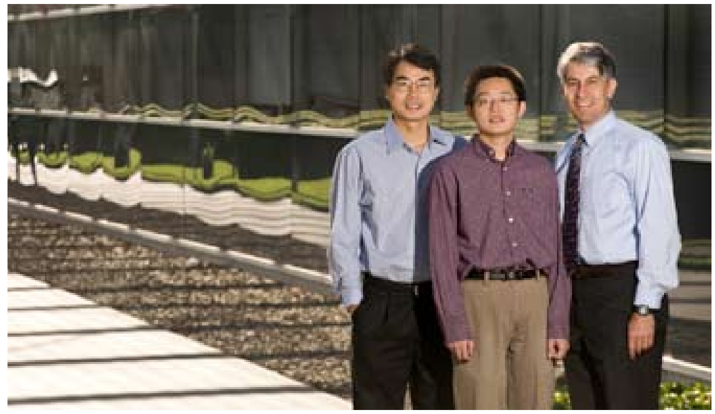
'Liposuction leftovers' easily converted to iPS cells



Globs of human fat removed during liposuction conceal versatile cells that are more quickly and easily coaxed to become induced pluripotent stem cells, or iPS cells, than are the skin cells most often used by researchers, according to a new study from Stanford's School of Medicine.

"We've identified a great natural resource," said Stanford surgery professor and co-author of the research, Michael Longaker, MD, who has called the readily available liposuction leftovers "liquid gold." Reprogramming adult cells to function like embryonic stem cells is one way researchers hope to create patient-specific cell lines to regenerate tissue or to study specific diseases in the laboratory.

"Thirty to 40 percent of adults in this country are obese," agreed cardiologist Joseph Wu, MD, PhD, the paper's senior author. "Not only can we start with a lot of cells, we can reprogram them much more efficiently. Fibroblasts, or skin cells, must be grown in the lab for three weeks or more before they can be reprogrammed. But these stem cells from fat are ready to go right away."

The fact that the cells can also be converted without the need for mouse-derived "feeder cells" may make them an ideal starting material for human therapies. Feeder cells are often used when growing human skin cells outside the body, but physicians worry that cross-species contamination could make them unsuitable for human use.

The findings were published in the Proceedings of the National Academy of Sciences. Longaker is the deputy director of the Stem Cell Institute and director of children's surgical research at Lucile Packard Children's Hospital. Wu is an assistant professor of cardiology and radiology, and a member of Stanford's Cardiovascular Institute.

"These cells are not as far along on the differentiation pathway, so they're easier to back up to an earlier state," said first author and postdoctoral scholar Ning Sun, PhD, who conducted the research in both Longaker's and Wu's laboratories. "They are more embryonic-like than fibroblasts, which take more effort to reprogram."

"The idea of reprogramming a cell from your body to become anything your body needs is very exciting," said Longaker, who emphasized that the work involved not just a collaboration between his lab and Wu's, but also between the two Stanford institutes.

"The field now needs to move forward in ways that the Food and Drug Administration would approve —with cells that can be efficiently reprogrammed without the risk of cross-species contamination—and Stanford is an ideal place for that to happen."

In addition to Sun, Wu and Longaker, other Stanford collaborators on the research include postdoctoral scholars Nicholas Panetta, MD, Deepak Gupta, MD, and Shijun Hu, PhD; graduate student Kitchener Wilson; medical student Andrew Lee; research assistant Fangjun Jia, PhD; associate professor of pathology and of pediatrics Athena Cherry, PhD; and professor of cardiothoracic surgery Robert Robbins, MD.

Read more at: stemcell.stanford.edu

Photography in This Issue
P. 1 Clarke Lab (top), Christopher Vaughan (middle), Majed (bottom)
P. 2 Mark Estes Photgraphy (top), Majed (bottom)
P. 3 Clarke Lab
P. 4 Alan Yatagai
P. 5 Majed
P. 7 Alan Yatagai
P. 8 Steve Fisch Photography