



Self-Renewal's Two Faces

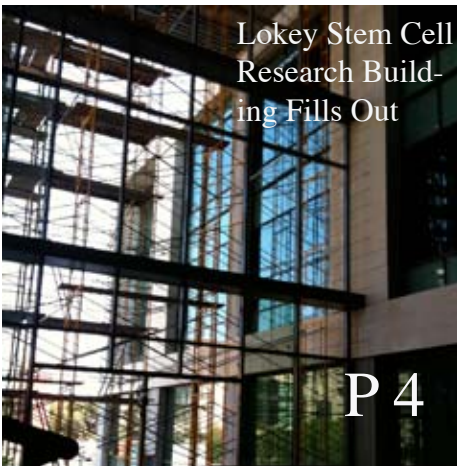
Researchers find a common regulatory pathway in normal breast stem cells and breast cancer stem cells.

P 3



Institute for Stem Cell Biology
& Regenerative Medicine

SEP 2009



Lokey Stem Cell
Research Building
Fills Out

P 4



Stem Cell
Training Class

P 2

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

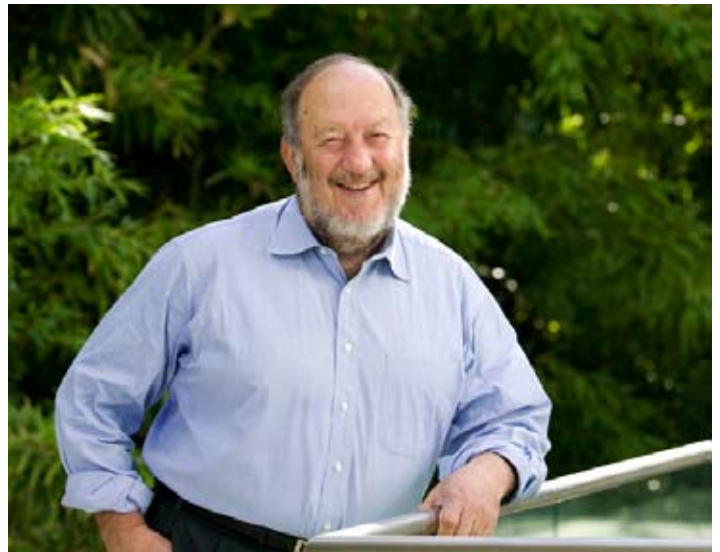
Continued Page 2

Continued from page 1

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 clearing 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>



Self Renewal's Two Faces

Researchers find a common regulatory pathway in normal breast stem cells and breast cancer stem cells.

Researchers at the School of Medicine have discovered, for the first time, a common molecular pathway that controls reproduction in both normal stem cells and cancer stem cells.

In a paper published Aug. 7 in the journal *Cell*, Michael Clarke, MD, the Karel H. and Avice N. Beekhuis Professor in Cancer Biology, and his colleagues showed that breast cancer stem cells and normal breast stem cells turn down the creation of a specific group of cell signals when they are reproducing. Increasing the amount of one of these signals, called miR-200c, strongly suppressed the ability of both cancer stem cells and normal stem cells to divide and reproduce.

The discovery of a common regulatory pathway in both kinds of stem cells supports the idea that cancer stem cells and normal stem cells share fundamental properties. "This very strongly supports the cancer stem cell hypothesis," said Clarke, who is associate director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and a member of the Stanford Cancer Center. "A lot of people have speculated that there was this molecular link between these two kinds of cells (cancer stem cells and normal stem cells), but this is the first time we have actually identified it."

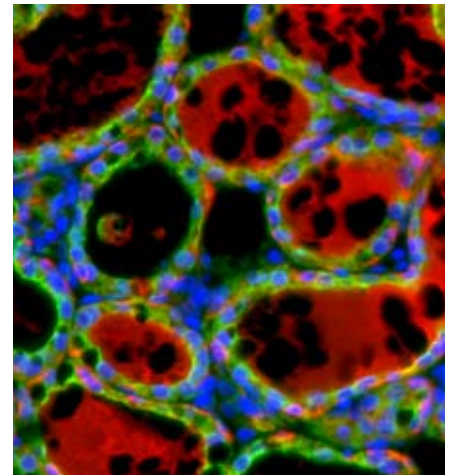
While the current discovery is important evidence of how cancer stem cells operate, it does not automatically lead to new cancer therapies. "The problem is that if we attack cancer using this mechanism, it is also going to affect normal stem cells which are essential for our survival," Clarke said. But understanding how cancer cells sustain themselves may in the future offer new ways of attacking the disease. "The hope is that we can find nuances that distinguish between how normal stem cells renew themselves and how cancer stem cells do so, and then use those differences to attack only the cancer," said Clarke.

The research also demonstrates the power of conducting studies that zero in on cancer stem cells rather than screen all cancer tumor cells. In the past,

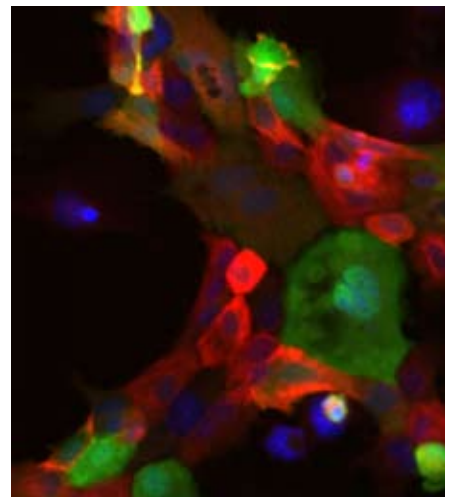
for instance, scientists tried to gain insight into how cancer cells reproduce by looking at molecular signals in all the cancer cells in a tumor. But this molecular detective work did not reveal cancer stem cells' use of the miR-200c pathway, probably because signals from cancer stem cells were lost in a crowd of molecular signals from the far more numerous non-stem cells. Clarke and his colleagues therefore isolated the cancer

stem cells first and then did the analysis. Clarke noted that it is technically challenging to isolate cancer stem cells, which can be outnumbered by generic tumor cells 100 to 1, but the rewards can be dramatic. By analyzing only stem cells, the link between the molecular signals that control reproduction in cancer stem cells and normal stem cells became apparent.

Read more at: stemcell.stanford.edu



Normal Breast Cells



Breast Cancer Stem Cells

Leukemia cells evade immune system by mimicking normal cells, Stanford study shows

STANFORD, Calif. — Human leukemia stem cells escape detection by co-opting a protective molecular badge used by normal blood stem cells to migrate safely within the body, according to a pair of studies by researchers at Stanford University Medical School. “We call it the ‘Don’t eat me signal,’” said Ravindra Majeti, MD, PhD, assistant professor of hematology at the medical school and the co-first author of one of the studies, which focused on acute myeloid leukemia. Patients whose cancer stem cells express higher levels of the molecule have a poorer prognosis than those whose cells express lower levels, and masking its presence makes the human cancer cells less deadly and more vulnerable to destruction when injected into mice. The results indicate that the molecule may serve both as a prognostic factor and a valuable therapeutic target for patients with the cancer.

“When we blocked this signal in mice with established human leukemia, the cancer cells were more easily removed by the body’s natural defenses,” Majeti said. The researchers are now moving ahead with plans to test a similar treatment in humans and have filed for a patent for the potential therapy.

Irving Weissman, MD, the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research at the medical school, is the senior author of both studies, published together in the July 24 issue of the journal *Cell*. Majeti shares his first authorship with Mark Chao, an MD and PhD student in the cancer biology program at the medical school. Both Majeti and Weissman are members of Stanford’s Cancer Center. Together, the researchers of the studies found that the molecule, CD47, protects the leukemia stem cells from macrophages — part of a roving cellular army tasked with finding and engulfing diseased or dying cells — by binding to a molecule on the macrophage’s surface. The interaction between the two proteins inhibits the macrophage’s killing instinct and allows the marauding cancer cells to escape unscathed.

In further study of the high-CD47 cancer stem cells

in a culture dish, researchers added an antibody that blocks the interaction of the cancer cells with macrophages — essentially hiding the protective badge. This allowed the macrophages to engulf the cancer cells. A similar treatment in mice inhibited the human cancer cells’ ability to cause leukemia and even prolonged the survival of mice with previously established leukemias.

“This was the real kicker,” said Majeti. “These mice showed a profound clinical response.” Majeti and his colleagues are now planning to craft a similar antibody for use in human clinical trials.

In addition to Majeti, Chao, Jaiswal and Weissman, other Stanford researchers involved in the studies include medicine instructor Ash Alizadeh, MD, PhD; graduate students Wendy Pang and Kenneth Gibbs, Jr.; former post-doctoral fellow Catriona Jamieson, MD, PhD; and pathology instructor Chris Park, MD. The research was funded by the National Institutes of Health, the Leukemia Society, the Ludwig Institute and the Smith Family Fund.

Read more at: stemcell.stanford.edu



Ravindra Majeti, MD

Center for Human
Embryonic Stem Cell
Research and Education

hESC

NEWS

Stanford Researchers get CIRM Grant to Break Bottleneck in Parkinson's Disease Research

Two stem cell researchers at Stanford and scientists at the Parkinson's Institute in Sunnyvale, CA, have received a large award from the California Institute for Regenerative Medicine (CIRM) to develop research that may overcome a major bottleneck in Parkinson's disease (PD) research and drug discovery.

As part of a joint venture with the Parkinson's Institute, Professor of Obstetrics and Gynecology Renee Reijo-Pera, PhD, and Professor of Neurosurgery Theo Palmer, PhD, were awarded the grant to develop induced pluripotent stem cells (iPS cells) from patients who have Parkinson's disease. The iPS cells will be generated by taking skin cells from Parkinson's patients and using specific genetic factors to reset those cells to an embryonic-like state.

These newly created stem cells, which carry the genetic code of known Parkinson's disease patients, can be grown in such a way that they turn into nerve cells. In some cases, the patients carried genes that cause PD and these cells will likely be affected PD pathology. In other cases, the cause was unknown and the cells will therefore be useful as a model system that allows researchers to study how Parkinson's disease develops in the first place and to test potential medications for the disorder.

Currently there are no good cellular models of PD, which is a major bottleneck to further research. "If we are successful, these cells would break this bottleneck and could immediately be used for a wide range

of clinical applications," says Reijo Pera. "This is an essential avenue for research if we want to offer our patients a new therapeutic approach that can give them a near normal life after being diagnosed with this progressively disabling disease."

Palmer adds that by partnering with Dr William Langston, Director and CEO of the Parkinson's Institute and Dr. Birgitt Schuele, a specialist in the genetics of PD, "we have put together a team that provides all the necessary elements to use this cutting edge technology in the discovery and application of new treatments for Parkinson's disease."



Renee Reijo Pera, PhD

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 department of hematology.

‘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.

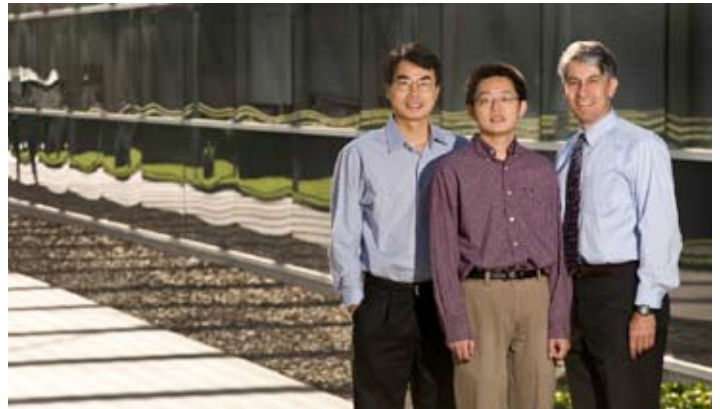
“We’ve identified a great natural resource,” said Stanford surgery professor and co-author of the research, Michael Longaker, MD, who has called the readily available liposuction leftovers “liquid gold.” Repro-

gramming 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 Photography (top), Majed (bottom)
P. 3 Clarke Lab
P. 4 Alan Yatagai

P. 5 Majed

P. 7 Alan Yatagai

P. 8 Steve Fisch Photography