

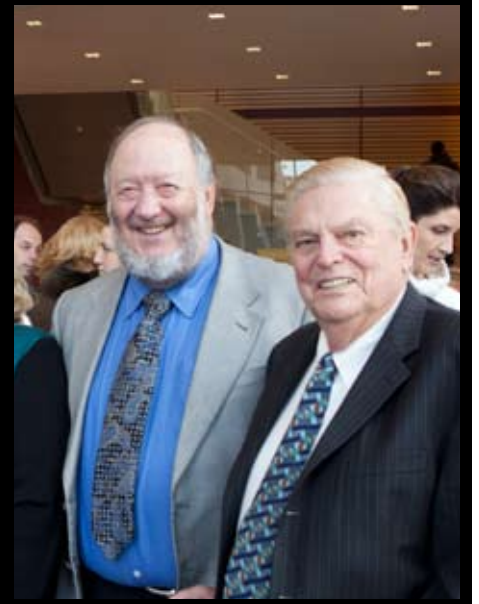


STANFORD
M E D I C I N E

Institute for Stem Cell Biology
and Regenerative Medicine



2010 Annual Report



Director's Statement

We are engaged in a grand experiment. In 2010 we moved into the Lorry I. Lokey Stem Cell Research Building, largest stem cell research building in the world, a building without departments and those other traditional barriers that unwittingly impede freedom of thought and action. Traditionally, basic science discoveries have come from basic science departments, and whether and when those discoveries are even thought to hold the potential to lead to therapies has not been considered the province of basic science departments. Such discoveries were to be picked up by biotech or pharma, and clinical trials and therapies hopefully would result, completely removed from the discoverers and from Stanford.

Here we begin with another premise: we will provide havens for insights that may not come from conventional wisdom, and we will provide partners in many disciplines so that experiments that lead to discoveries will be devised. But unlike departments, we will not stop there. We will mix in physician-scientist colleagues who every week meet the challenges of incurable diseases in patients who, like all of us, still have hopes and dreams to fulfill. Together we will test the translational ideas that can lead to the proof-of-principle tests that best approximate the diseases we study.

Given proof-of-principle tests in animals and wise funding free of profit motive, we hope to take these proofs to clinical trials, carried out by our physician scientists working with scientific physicians at Stanford. From these trials, hopefully, a few will emerge to change how we understand and treat diseases. Many of these will follow a new therapeutic principle: a single treatment with self-renewing stem cells that regenerate the diseased tissues for life, rather than daily treatments with drugs that ameliorate the disease but do not cure it. Only when the course of these discoveries, translation, and clinical trial successes make the path unquestionably robust will we hand them over to those who can make them available to all who need them.



A handwritten signature in black ink, which appears to read "Irving L. Weissman". The signature is fluid and cursive, with a prominent initial "I".

Irving L. Weissman
Director

2010 Annual Report

Table of Contents

Director's Statement

Institute Members and Associate Members

The Lorry I. Lokey Stem Cell Building

Research

Embryonic and iPS

Cancer Stem Cells

Tissue-Specific Stem Cells

Seibel Center and Scholars

Program in Regenerative Medicine

Education

PhD Program

CIRM Training Program

Funding

Grants of 2010



Irving Weissman, MD

Director

Director of the Ludwig Center for Cancer Stem Cell Research
Virginia and D.K. Ludwig Professor for Clinical Investigation and
Cancer Research

Irving Weissman has directed the institute since its founding, providing vision and leadership to build one of the nation's top stem cell programs. In 1988, Dr. Weissman became the first researcher to isolate in pure form any stem cell in any species when he found hematopoietic (blood-forming) stem cell in mice. He subsequently found the human hematopoietic stem cell, the human neuronal stem cell, and the human leukemia stem cell. His work has opened up an entirely new area of scientific research with enormous potential for life-saving therapies.

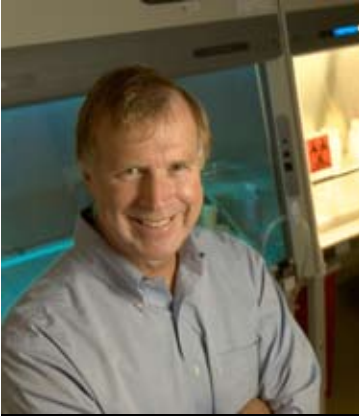


Michael T. Longaker, MD, MBA, FACS

Co-Director

Director, Program in Regenerative Medicine
Deane P. and Louise Mitchell Professor

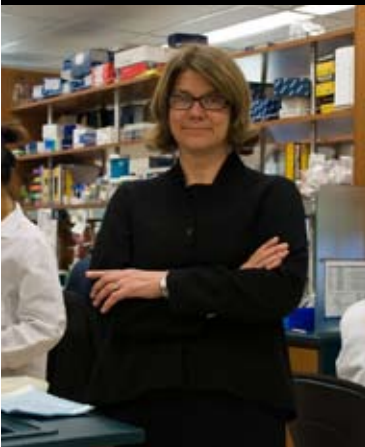
Michael Longaker has broad experience in pediatric plastic surgery, developmental biology, epithelial biology, tissue repair, and tissue engineering. He has extensive research experience in the cellular and molecular biology of extracellular matrix, with specific applications to the differences between fetal and post-natal wound healing, the biology of keloids and hypertrophic scars, and the cellular and molecular events that surround distraction osteogenesis with respect to craniofacial development. Most recently, his research has focused on multipotent mesenchymal cells derived from adipose tissue and their applications for tissue repair, replacement, and regeneration.

**Michael F. Clarke, MD**

Associate Director

Karel H. and Avice N. Beekhuis Professor in Cancer Biology

In addition to his clinical duties in cancer treatment, Michael Clarke maintains a laboratory focused on stem cells and the role they play in cancer. Dr. Clarke's research is aimed at the identification and characterization of cancer stem cells, and at increasing our knowledge of the factors that control self-renewal in normal stem cells and their malignant counterparts. Dr. Clarke was the first researcher to find cancer stem cells in a solid tumor (breast cancer) and discovered that the inhibition of programmed cell death is essential for the growth of breast cancers.

**Renee Reijo Pera, PhD**

Director, the Center for Human Embryonic Stem Cell Research and Education

Renee Reijo Pera focuses on understanding human embryo growth and development, and on characterizing the basic properties of human embryonic stem cells, especially their ability to generate pluripotent stem cells, somatic cells, and germ cells. Her early work resulted in identification of one of the first genes specifically implicated in human germ cell development. Subsequently, her laboratory has established techniques for differentiation of human embryonic stem cells to germ cells and genetic manipulation of the pathways.



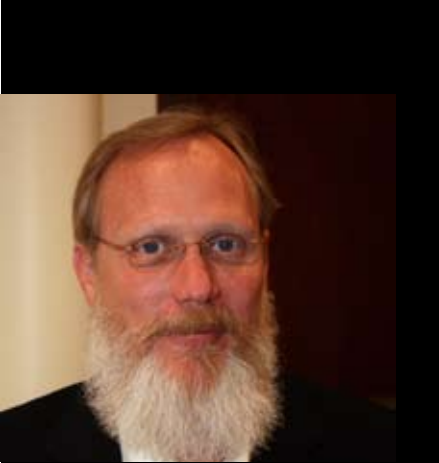
Phillip A. Beachy, PhD

Phillip Beachy studies the function of Hedgehog proteins and other extracellular signals in morphogenesis (pattern formation) and in injury repair and regeneration (pattern maintenance). The Beachy lab studies how the distribution of such signals is regulated in tissues, how cells perceive and respond to distinct concentrations of signals, and how such signaling pathways arose in evolution. He also studies the normal roles of such signals in stem-cell physiology and their abnormal roles in the formation and expansion of cancer stem cells.



Marius Wernig, MD

Marius Wernig is interested in two major areas of stem cell biology. One focus is the epigenetic reprogramming of somatic cells into pluripotent stem cells, and this technique's translational applications for regenerative medicine. Another area of interest is the study of self-renewal mechanisms of mammalian neural progenitor cells, with the hope of identifying novel approaches to better understand brain cancer. Recently, he has published notable research on the direct transformation of skin cells into nerve cells.

**Theo Palmer, PhD**

The research of the Palmer lab examines how neural stem cells respond to cues in order to add and integrate new neurons into a functional circuit. His studies of neurogenesis in the developing brain focus on the influence of maternal health or illness on fetal brain development. Studies of stem cells in the adult focus on the hippocampus, one of the few areas where neurogenesis naturally continues throughout life. The Palmer lab is now able to use human embryonic stem cells and non-embryonic, induced pluripotent stem cells to generate several types of human neurons.

**Ravindra Majeti, MD, PhD**

Ravindra Majeti focuses on the molecular characterization and therapeutic targeting of leukemia stem cells in human hematologic disorders, particularly acute myeloid leukemia (AML). The Majeti lab is also interested in developing a similar characterization of normal human hematopoiesis and hematopoietic stem cells. A major focus of the lab is the identification of cell surface molecules preferentially expressed on leukemia stem cells and the development of therapeutic monoclonal antibodies targeting these proteins. Toward this goal, together with Irv Weissman, the lab is actively developing an anti-CD47 antibody for clinical trials in human AML.

**Maximillian Diehn, MD, PhD**

Max Diehn's research focuses on cancer stem cell biology and its implications for cancer therapy. He is interested in developing a deeper molecular understanding of cancer stem cells, including identifying pathways and genes important for their survival and self renewal. Additionally, work in the Diehn lab is aimed at overcoming resistance mechanisms to radiotherapy and chemotherapy in cancer stem cells. Dr. Diehn is a radiation oncologist and specializes in the treatment of lung cancer and stereotactic body radiation therapy.

Members:

Beachy, Phil
Developmental Biology

Clarke, Michael
Medicine/Oncology

Diehn, Maximillian
Radiation Oncology

Longaker, Michael
Surgery/Plastic & Reconstructive

Majeti, Ravindra
Medicine/Hematology

Palmer, Theo
Neurosurgery

Reijo Pera, Renee
Obstetrics and Gynecology

Weissman, Irving
Pathology

Wernig, Marius
Pathology

Barres, Ben
Neurobiology

Barron, Annelise
Bioengineering

Behr, Barry
Obstetrics and Gynecology

Berg, Paul
Biochemistry

Bergmann, Dominique
Biology

Blau, Helen
Microbiology & Immunology

Bogyo, Matthew
Pathology

Brunet, Anne
Genetics

Butte, Atul
Medicine/Pediatrics

Calos, Michele
Genetics

Associate Members:

Altman, Russ
Bioengineering

Andreasson, Katrin
Neurology

Artandi, Steve
Medicine/Hematology

Attardi, Laura
Radiation Oncology

Axelrod, Jeffrey
Pathology

Baker, Bruce
Biology/Emeritus

Baker, Julie
Genetics



Chang, Ching-Pin
Medicine/Cardiovascular Medicine

Chang, Howard
Dermatology

Chen, Chang-Zhen
Microbiology & Immunology

Chen, James
Chemical & Systems Biology

Cheng, Ivan
Orthopaedic Surgery

Clandinin, Thomas
Neurobiology

Cleary, Michael
Pathology

Cochran, Jennifer
Bioengineering

Cooke, John P.
Medicine/Cardiovascular Medicine

Deisseroth, Karl
Bioengineering

Elias, Joshua
Chemical & Systems Biology

Engleman, Edgar
Pathology

Feldman, Brian
Pediatrics

Ferrell, James
Chemical & Systems Biology

Fontaine, Magali
Pathology

Fuller, Margaret
Developmental Biology

Giaccia, Amato
Radiation Oncology

Gonzalzo, Mark
Urology

Gozani, Or
Biology

Graef, Isabella
Pathology

Gurtner, Geoff
Surgery/Plastic and Reconstructive
Surgery

Hanawalt, Philip
Biology

Heilshorn, Sarah
Materials Science & Engineering

Heller, H Craig
Biology

Heller, Stefan
Otolaryngology

Helms, Jill
Surgery/Plastic and Reconstructive
Surgery

Hsu, Teddy
Obstetrics and Gynecology

Kennedy, Donald
Honorary Member

Khavari, Paul
Dermatology

Kim, Seung K.
Developmental Biology

Kovacs, Gregory
Electrical Engineering

Krasnow, Mark
Biochemistry

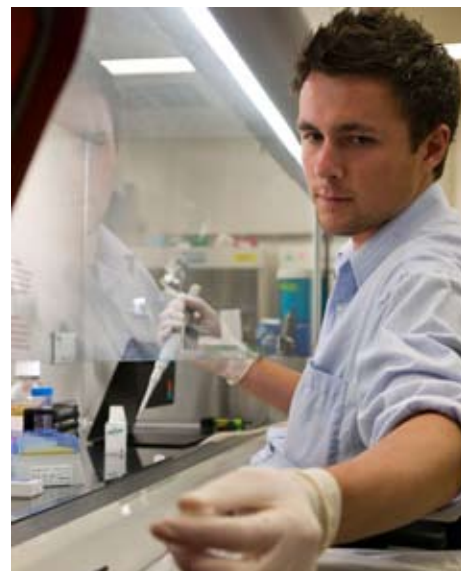
Kuo, Calvin
Medicine/Hematology

Levenston, Marc
Mechanical Engineering

Liao, Yaping
Ophthalmology

Lipsick, Joseph
Pathology

Lowe, Anson
Medicine/Gastroenterology and
Hepatology



Lu, Bingwei
Pathology

Luo, Liqun
Biology

Malenka, Robert
Psychiatry & Behavioral Sciences

McConnell, Susan
Biology

Mitchell, Beverly
Medicine/Oncology

Nusse, Roel
Developmental Biology

Oro, Anthony
Dermatology

Pasricha, Pankaj Jay
Medicine/Gastroenterology and
Hepatology

Peehl, Donna
Urology

Penn, Anna
Pediatrics /Neonatology

Quake, Stephen
Bioengineering

Rando, Thomas
Neurology

Recht, Lawrence
Neurology

Reiss, Allan
Psychiatry and Behavioral Science

Rosen, Glenn
Medicine/Pulmonary & Critical
Care Medicine

Rutt, Brian
Radiology/Diagnostic Radiology

Sage, Julien
Pediatrics/Cancer Biology

Schnitzer, Mark
Biology & Applied Physics

Scott, Matt
Developmental Biology

Shizuru, Judith
Medicine/ Blood and Bone Marrow
Transplantation

Shortliffe, Linda
Medicine/Urology

Simon, Michael
Biology

So, Samuel
General Surgery

Stearns, Tim
Biology





Steinberg, Gary
Neurosurgery

Sudh f, Thomas
Molecular and Cellular Physiology

Sunwoo, John
Otolaryngology

Sweet-Cordero, Alejandro
Pediatrics/Cancer Biology

Talbot, William
Developmental Biology

Wandless, Thomas
Chemical & Systems Biology

Weinberg, Kenneth
Pediatrics

Wong, Albert
Neurosurgery

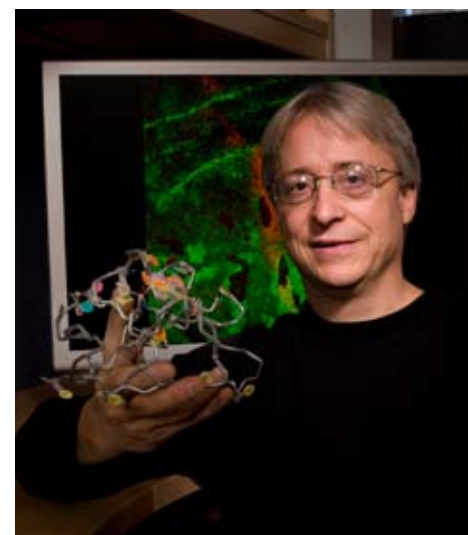
Wu, Joseph
Medicine/Cardiovascular Medicine

Wysocka, Joanna
Chemical & Systems Biology

Yang, Phillip
Medicine/Cardiovascular Medicine

Yock, Paul
Medicine/Cardiovascular Medicine

Siebel Scholars:
Luke Lee
Debashis Sahoo
Hiroo Ueno





Throughout the fall of 2010, stem cell researchers and staff from three

Stanford Institutes of Medicine moved into the new Lorry I. Lokey Stem Cell Research Building. At the official dedication on October 27, researchers, donors, and university and state officials gathered to Stanford School of Medicine's newest building.



When fully occupied, the Lokay building's 200,000 square feet of interior space will be home to 33 laboratories and over 500 scientists, students and fellows. The building is designed to foster creativity and productivity in stem cell science. Research space is organized into "neighborhoods" of common interest to promote collaboration. The building has extensive research support space and advanced facilities, including the Human Embryo, Oocyte, Human Embryonic Stem Cell And Somatic Cell Bank, the Human Embryology, Human Embryonic Stem Cell And Nuclear Reprogramming Education Core, the Microfluidics Laboratory , the Flow Cytometry Core, the Cancer Tissue Bank And Rapid Autopsy/Tissue Core, the Advanced In Vivo Imaging, and the Behavioral And Functional Neuroscience

Laboratory.

Another innovation designed into the building is the creation of 60 "hotel benches" where visiting scientists, engineers or physicians can work side-by-side with Lokey Building researchers for one to three years. Each hotel bench occupant must apply for the space and bring something unique and desirable to the building. The cross-disciplinary research fostered by these collaborations should speed basic research as well as its translation

to the clinic.

“This building was designed to be a research thoroughbred,” said Chris Shay, manager of capital projects at the School of Medicine. “It’s packed with details that make other faculty members envious.”



“We tried to mix the best elements of Beckman, CCSR and the Clark Center,” said project manager Jill Knapp. Each of the building’s 33 research laboratories is situated on the outside of the building, with ceilings that slope upward toward large windows to capture natural light. Lab benches have castors, and electrical and gas and vacuum lines descend from above to allow researchers some freedom to arrange their work space, while interior, linear equipment halls offer ample support space for freezers, centrifuges and other equipment. The building’s location and exterior appearance was also carefully planned. The facility rests

at one end of the Medical Promenade, which bisects CCSR and Beckman and leads to both Stanford Hospital & Clinics and Lucile Packard Children’s Hospital. Translational researchers in the building can spend their mornings in the clinic seeing patients and then walk to their labs within five minutes.



Robert Klein, chairman of the governing board of the California Institute for Regenerative Medicine, noted, “The Lorry I. Lokey Stem Cell Research Building at Stanford provides a world-class platform to extend the global impact of Stanford’s stem cell research on chronic disease and injury.”

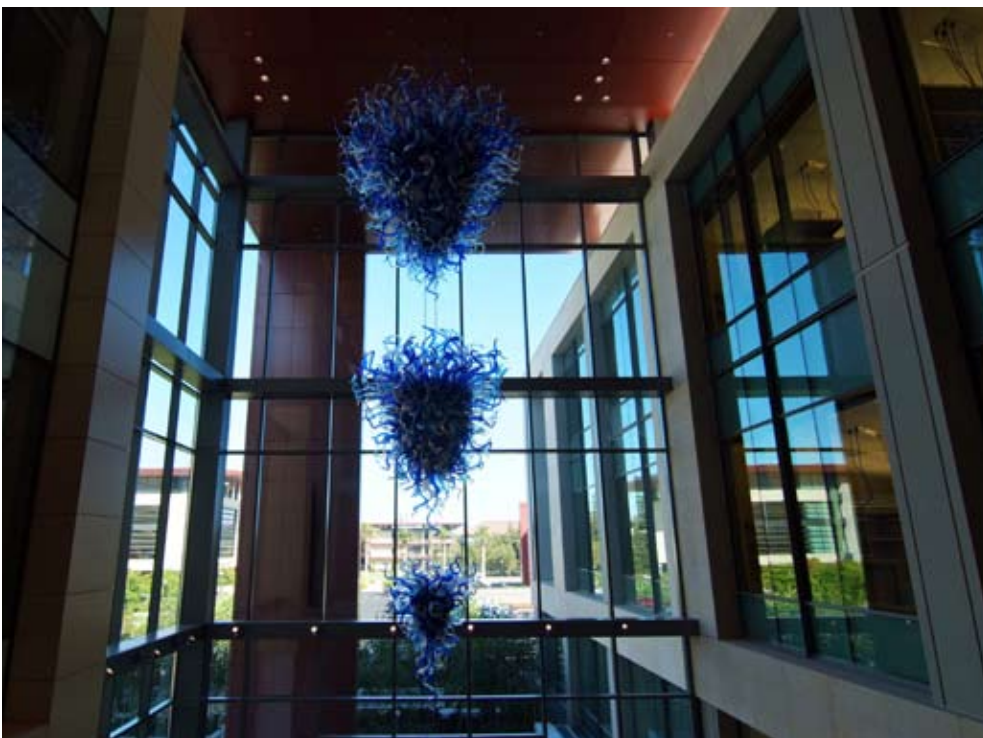


Even before researchers and staff moved into the Lorry I. Lokey Stem Cell Research Building, plans were in motion to bring artworks to the building. The goal, as Irv Weissman says, is “to make this house of science into a home that every day provides comfort and inspiration to the scientists, physicians, students and fellows who will spend most of their days and nights here.”

Weissman observes that artworks can inspire people in life’s activities, and provide important symbols that remind us why we do the work we do. With this in mind, a longtime goal has been to seed the building with paintings, prints, and sculpture. Planning for the largest piece, a two-ton Dale Chihuly sculpture called the Tre Stelle di Lapislazzuli Chandelier, was set in motion even before the foundation for the building was laid. Sue McCollum, whose non-profit My Blue Dots supports cancer research, began



discussions with Dale Chihuly about creating the sculpture. McCollum and the friends of My Blue Dots then donated the sculpture to the institute, creating a lasting and dramatic impression on those entering the front lobby.

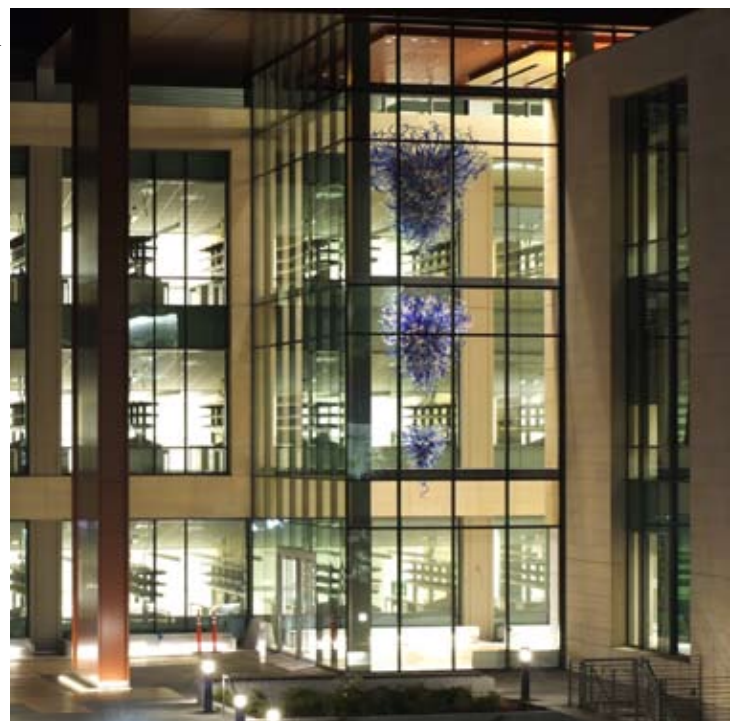




More recently, Irv Weissman began discussions with California artist Nathan Oliveira to bring his bronze sculpture *Universal Woman* into the building. Sadly, Oliveira died last year before arrangements could be finalized, but through the efforts of his son Joe Oliveira and the generosity of [Dunwoodies]. *Universal Woman* will grace the Lokey building in 2011. Additionally, Ann Bing has lent a number of paintings, prints, and photographs that now hang in offices and hallways throughout the building.

“Infusing the building with art in a variety of media and on all floors reminds us all of the importance of interaction

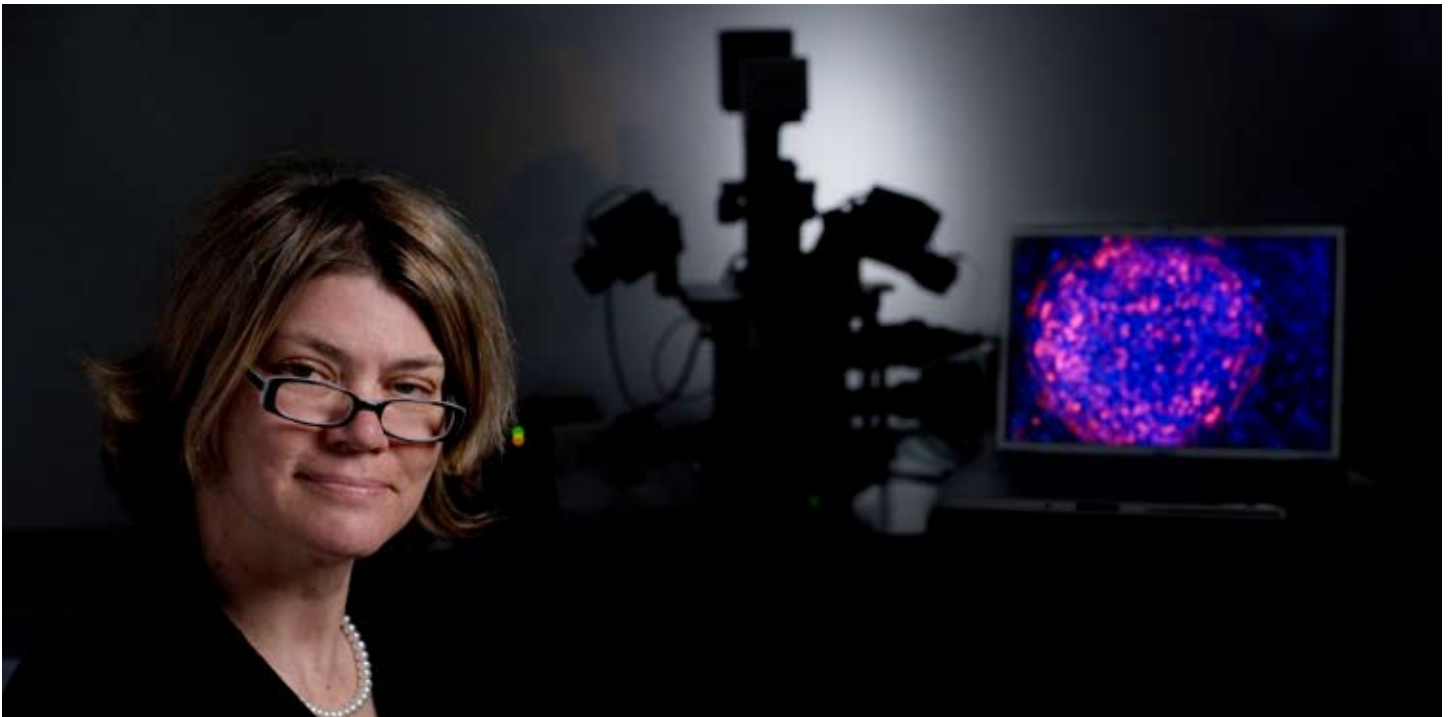
across disciplines, and that these creative interactions are going on in this place,” Weissman says. “We should remember that while the occupants of this building will change over time, the building and its symbolic art will remain. Art, like our discoveries and translations to therapies, will endure.”



Embryonic and Pluripotent Stem Cells

Understanding the Building Blocks of Life

Pluripotent stem cells—including totipotent embryonic stem cells—are the self-replicating cells that can give rise to all the specialized cells in the body. These cells are extremely versatile and can develop into any kind of organ or tissue, depending on their programming and the signals they receive from their environment. Understanding embryonic and pluripotent stem cells will likely provide the keys to creating new therapies for disease, repairing or replacing damaged organs, and solving problems in human reproduction. Because each cell type in the body can be created from stem cells, developing pluripotent stem cells may also reveal paths for creating tissue and organ-specific stem cells, many of which have yet to be discovered.



Research Highlights:

Earlier, more accurate prediction of embryo survival enabled by research

Two-thirds of all human embryos fail to develop successfully. Now, in a new study, researchers of Renee Reijo Pera, PhD, have shown that they can predict with 93 percent certainty which fertilized human eggs will make it to a critical developmental milestone and which will stall and die. The findings are important to the understanding of the fundamentals of human development at the earliest stages, which have largely remained a mystery despite the attention given to human embryonic stem cell research. Using a time-lapse video microscopy and computer software specially designed at Stanford, they 100 embryos for five to six days, they found the critical events that determine an embryo's success as it progresses from one cell to four cells within the first two days after fertilization.

Stanford joins first embryonic-stem-cell therapy clinical trial

The Stanford University School of Medicine and the Santa Clara Valley Medical Center became the third site involved in the first clinical trial of cells derived from human embryonic stems. The FDA-approved, phase-1 trial, run by Menlo Park-based Geron Corp., is aimed at treating people with recent spinal cord injuries. The company plans to enroll up to 10 patients with spinal cord injuries at up to seven institutions nationwide.

Virus-free technique enables scientists to easily make stem cells pluripotent, moving closer to possible human therapies

Researchers in the laboratories of Michael Longaker, MD, and Joseph Wu, MD, PhD, found a way to create iPS cells without using the viruses, which are traditionally used to induce pluripotency but can cause dangerous disruptions in the genome. Longaker and Wu instead used a plasmid, or loop of DNA, which carries the transformative genes into the cell but doesn't insert them into the genome. The technique has the potential to remove one hurdle to the therapeutic use of iPS cells in human patients.

The Center for Human Embryonic Stem Cell Research and Education

The Center for Human Embryonic Stem Cell Research and Education has become a powerful presence in the world of embryonic research because of its focus on human development. Although researchers around the world study embryonic stem cells from mice or other organisms, human embryonic stem cells can behave quite differently. Because the emphasis of the Center for Human Embryonic Research and Education is on research with human embryonic stem cells, research at the center is highly relevant to the effort to create medical therapies from stem cell research.

Scientists make neurons with symptoms of Parkinson's disease from patient's skin cells

Researchers at the Stanford created nerve cells from the skin of a woman with a genetic form of Parkinson's disease and showed that these cells had some key features of the neurodegenerative disorder. The scientists hope to use the neurons to learn more about Parkinson's and to test possible treatments. Such a tool is critical because there are no good animal models for Parkinson's disease. It also validates the use of induced pluripotent stem cells, or iPS cells, to model various diseases.

Researchers directly turn mouse skin cells into neurons, skipping IPS stage

Marius Wernig, MD discovered a new cocktail of genes that can convert mouse skin cells directly into neurons without passing through an intermediate pluripotent stage. This discovery opens the door to deeper study of many neurodegenerative and mental disorders, if the method is successfully applied to human cells.

Induced Pluripotent Stem (iPS) Cells

One of the most exciting discoveries in recent years was the finding that fully mature cells could have their genetic machinery reset to a nearly embryonic state through exposure to four specific factors. This technique has the potential to create pluripotent stem cells more easily and with more efficiency than with previous techniques. Furthermore, iPS techniques can be used to create stem cell populations that carry the disease-related genetic profiles of specific individuals, thereby providing a testing platform for understanding and treating those diseases.

**Skin cells help to develop possible heart defect treatment in first-of-its-kind study**

Using skin cells from young patients who have a severe genetic heart defect for which there are currently no good treatments. Scientists in the lab of Ricardo Dolmetsch, PhD, have generated beating heart cells that carry the same genetic mutation. The newly created human heart cells allowed the researchers for the first time to examine and characterize the disorder at the cellular level. The investigators used the cells to screen candidate drugs and found a promising drug that may reverse the heart defect.

Cancer Stem Cells

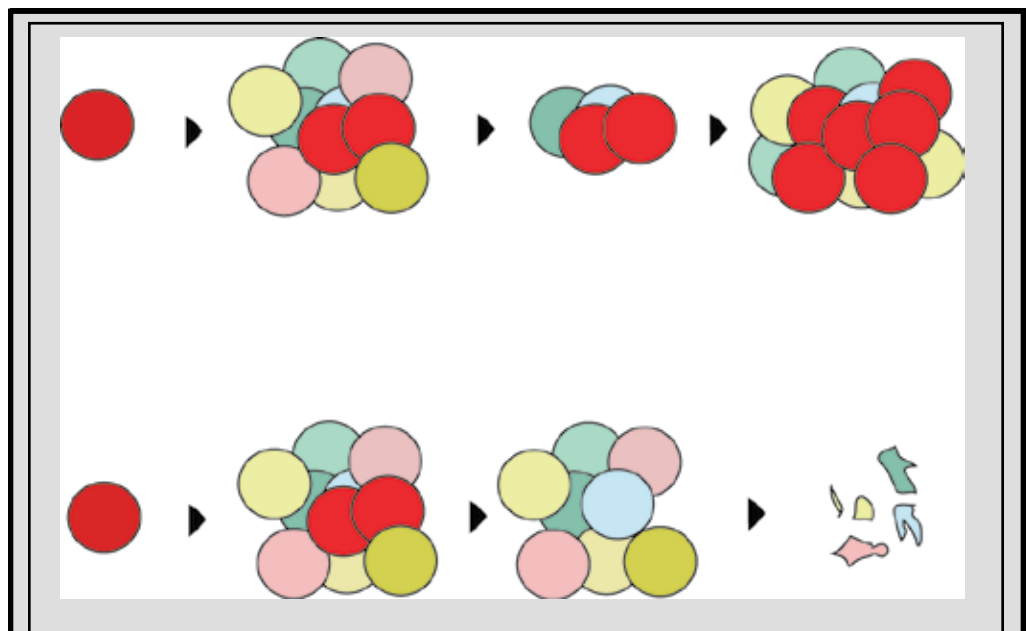
Attacking Cancer at the Root

The application of stem cell biology to cancer research is likely to have a profound impact on the future of cancer treatment. Researchers at the Institute for Stem Cell Biology and Regenerative Medicine are making progress on a number of fronts in understanding how cancer cells arise and spread, and in finding the cells' vulnerabilities that can be exploited in targeted treatments.

The cancer stem cell theory is that all cancers contain cancer stem cells that acquire or retain the self-replicating capabilities of stem cells, without the controls that usually regulate their growth. Just as stem cells represent a minority of all cells in the body, the cancer stem cells that initiate and drive malignancy may be a minority of the cells in a tumor or of the cells circulating in myeloid leukemia.

Effectively treating cancer requires attacking the cancer stem cells. Shrinking a tumor with drugs or beating back a leukemia will buy time, but curing a cancer likely will only come from destroying the cancer stem cells.

The institute has made significant progress in cancer stem cell research in 2009, due to the depth of experience in cancer biology and powerful collaborations with other Stanford faculty.



Two potential courses of cancer treatments, one (at top) in which cancer stem cells (CSCs, shown in red) are not targeted, and another (bottom) in which CSCs are specifically targeted. In the first case, failure to eliminate CSCs leads to a later resurgence of cancer. In the second case, when cancer stem cells are killed, the body's natural defenses eliminate the remaining cancer cells.

Researcher Highlights:**Anti-CD47 antibodies allow the body to attack lymphoma**

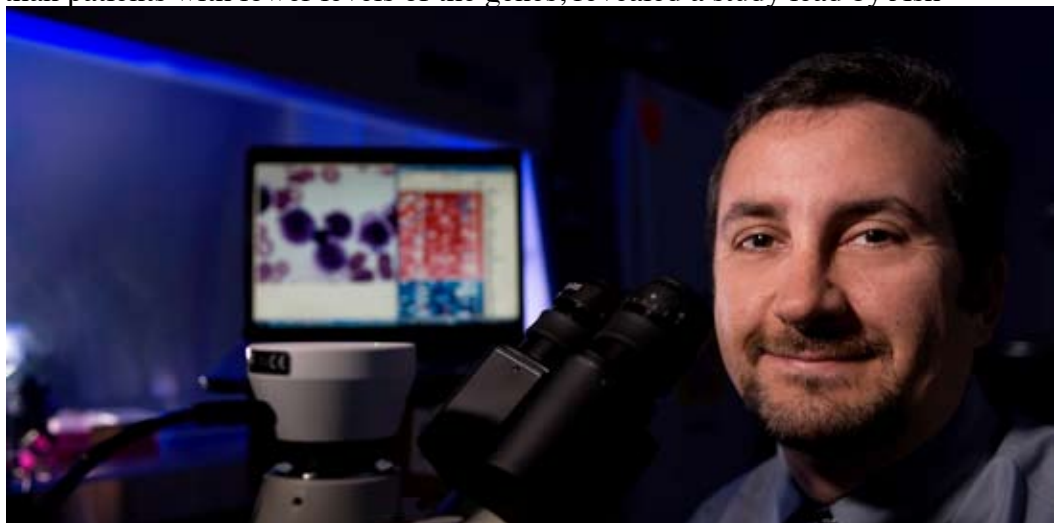
Continuing their pathbreaking research on CD47 and cancer, the Weissman and Majeti labs showed published results showing that when human non-Hodgkins lymphoma cells were transplanted into mice, treatment with an anti-CD47 antibody and rituximab, a previously FDA-authorized medication, led macrophage to envelop and destroy the cancer cells. The researchers demonstrated that this treatment could cured between 60% and 90% of the mice engrafted with non-Hodgkins lymphoma. They previously demonstrated that this treatment was effective against AML and bladder cancer, suggesting that it would be effective against a wide variety of cancers.

**Calreticulin is an “eat me” signal on most cancers**

Researchers in the Weissman and Majeti labs showed that most cancer cells carry the seeds of their own destruction. They revealed that calreticulin (CRT) on most kinds of cancer provides an “eat me” signal to circulating macrophage. They also showed that on cancer this signal is counteracted by CD47’s “don’t eat me” signal, thus protecting the cancer. Blocking CD-47 leads to phagocytosis of the cancer cells because it exposes CRT’s “eat me” signal. This system of cell signals explains why normal cells are not effected when CD47 is blocked.

Study demonstrates the pivotal role of stem cells in cancer

Leukemia patients whose cancers express higher levels of genes associated with cancer stem cells have a significantly poorer prognosis than patients with lower levels of the genes, revealed a study lead by Ash Alizadeh, MD, PhD. The finding is among the first to show that the cancer stem cell hypothesis can be used to predict outcomes in a large group of patients. The research strongly implies that the greatest success in fighting cancer will come from therapies that target cancer stem cells.



Discoveries offer first new hope in three decades for lethal pediatric brain tumor

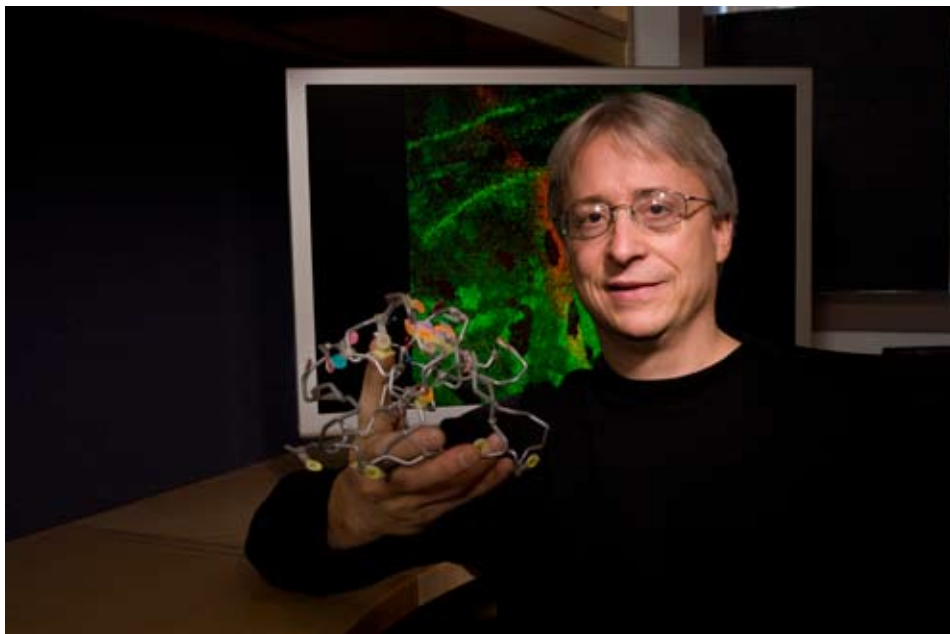
For the first time, scientists cultured human cells from this cancer, Diffuse Intrinsic Pontine Glioma, and used those cells to create an animal model of the disease. Their discoveries will facilitate research on new treatments for DIPG, a tumor of school-aged children that is now almost universally fatal. The team's early experiments supported the idea that the Hedgehog pathway is part of the pathology of DIPG, suggesting that it would be a good target for drugs.

Arsenic shows promise as cancer treatment

Arsenic trioxide has been used as a therapy for a particular type of leukemia for more than 10 years. Now researchers in the laboratory of Philip Beachy, PhD, have shown that it may be useful in treating a variety of other cancers. Combining arsenic with other therapies may give doctors a two-pronged approach to beating back forms of the disease caused by a malfunction in the Hedgehog pathway, a critical cellular signaling cascade.

Antifungal medicine shown to slow tumor growth in mice

A study in the Beachy lab revealed that a common antifungal medication can slow tumor growth in mice. The drug, called itraconazole, inhibits the action of the Hedgehog pathway, which is important during both fetal development and cancer progression. Because it works at dose levels already approved for use in humans, clinical trials in patients may not be far off. The researchers applied about 2,400 drugs to cells specially engineered by Beachy to emit a light signal when the Hedgehog pathway is active. Most of their several dozen candidates either required doses too high to be achieved in humans or would be dangerous for long-term use. But itraconazole showed promise.



Melanoma-initiating cells identified

Scientists at the School of Medicine have identified a cancer-initiating cell in human melanomas. The finding by Maximillian Diehn, MD, PhD, is significant because the existence of such a cell in the aggressive skin cancer has been a source of debate. The researchers also found that current immunotherapies do not target the melanoma stem cells, but instead target their daughter cells, which may explain why such therapies have been largely unsuccessful in preventing melanoma recurrence in human patients.

Tissue-Specific (Adult) Stem Cells

Studying the Framework of Future Therapies

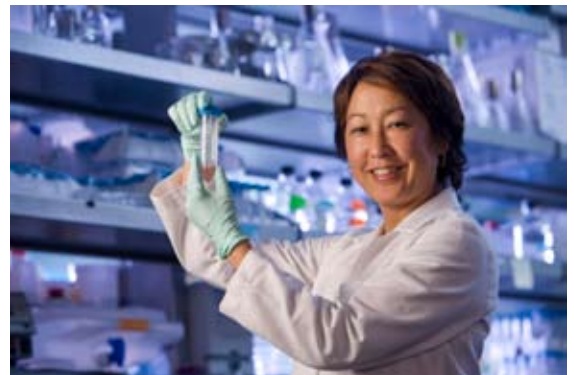
Embryonic stem cells are totipotent--able to become any kind of cell in the body. As an organism grows, however, stem cells become more specialized. After the initial developmental process, every organ and tissue in the body is regenerated by these tissue-specific stem cells. Skin stem cells renew the layers of skin that we constantly slough off. Blood stem cells in the bone marrow continually replenish our supply of blood and immune cells. Even the brain has neural stem cells that create new neurons and support cells, although infrequently. These tissue specific stem cells are called “adult” stem cells because they operate throughout life, even though they are also present in children.

Learning how these cells operate will help us bolster our natural regenerative abilities. In addition, many of the signs and symptoms of aging are mostly due to the declining ability of stem cells to renew tissues and organs as they are supposed to do.

Research Highlights:

Purified blood stem cells improve success of bone marrow transplants in mice, study shows

Researchers in the lab of Judith Shizuru, MD, PhD have challenged decades of accepted wisdom about bone marrow transplantation with a new study showing that mice receiving purified blood stem cells are less prone to complications than mice receiving stem cells plus purified T cells. Conventional wisdom among transplantation specialists has been that the bone marrow transplant should contain some T cells from the donor. When Shizuru and her colleagues compared mice given pure stem cells with mice given a mixture of stem cells and mature T cells, they found that the mice given pure stem cells were better at forming new blood cells and faster in regenerating lymphoid tissues.



New center for research on aging established with grant from Glenn Foundation

The Glenn Foundation for Medical Research has awarded a \$5 million grant to Stanford University to launch a new center on the biology of aging, focusing on the role of stem cells in the aging process.

At the new Paul F. Glenn Laboratories for the Biology of Aging at Stanford, researchers will look at how stem cells change as an individual ages and how that contributes to the development of age-related diseases and disorders. “There is something about age that predisposes us to disease,” said Thomas Rando, MD, PhD, a

professor of neurology and neurological sciences who will serve as the director of the new center. “If we could somehow figure out the mechanisms of aging and are able to intervene, it would potentially offer therapy to a wide variety of diseases — not just cancer, heart disease or Alzheimer’s, but all of them.”

Interdisciplinary Research

Computer scientist and Siebel Scholar Debashis Sahoo, working with David Dill (Computer Science), Sylvia Plevritis (Radiology), and Jun Seita, Deepa Bhattacharya and Matt Inlay in the Weissman laboratory, has shown that Boolean search strategies can reveal the presence of completely new and unknown stem cell control molecules. Sahoo asks researchers to supply the names of two marker genes, one of which is expressed by a stem cell and one of which is expressed by a more differentiated or adult cell. Sahoo then uses Boolean searches of existing databases to find the genes that are transiently expressed in the same developmental pathway. Using this method, Sahoo has identified many new molecules and genes that are associated with stem cell development.



Aiming to cure deafness, scientists first to create functional inner-ear cells



After years of lab work, researchers in the laboratory of Stefan Heller, PhD reported that they found a way to develop mouse cells that look and act just like the animal’s inner-ear hair cells — the linchpin to our sense of hearing and balance — in a petri dish. If they can further perfect the recipe to generate hair cells in the millions, it could lead to significant scientific and clinical advances along the path to curing deafness in the future, they said.

New Doctoral Program in Stem Cell Biology and Regenerative Medicine

During 2010, the institute laid the groundwork for the creation of a doctoral program in stem cell biology and regenerative medicine, which will be the first PhD program in stem cell biology in the country and the first new interdisciplinary doctoral program at Stanford School of Medicine in 20 years. The PhD program, with a master's degree option, is on track for university approval and is slated to start accepting student applications in the fall of 2011.

The foundation of a doctoral program in stem cell biology and regenerative medicine is a recognition of the unique perspectives, orientation and training inherent to the discipline.

“Stem cell biology as a field includes a scope of knowledge and a skill set that is not covered by other disciplines,” says Renee Reijo Pera, PhD, director of the new doctoral program. “When you are studying developmental biology you are looking at the development of tissue, but stem cell biology is also concerned with the maintenance of tissues; much of aging can be traced to the functional loss of a pool of stem cells, which is not covered at all by developmental biology.”

The inclusion of regenerative medicine in the program also recognizes the discipline's interest in moving basic science findings from the laboratory into the clinic. “This translational component is not really an inherent part of programs like developmental biology, molecular biology or genetics,” notes Reijo Pera.

The new degree program will appeal strongly to a new generation of graduate students who are very much interested in applying their discoveries. “Students used to be content simply studying the basic biological sciences, but a lot of students now want to bring that work forward to address critical clinical needs,” Reijo Pera says. “They are interested in changing the world.”



Renee Reijo Pera, PhD

CIRM Training Grants

The institute administers a CIRM-funded training grant for full-time research and can fund the scholar for up to three years. The program includes several unique requirements that make it particularly valuable. For instance, the scholar's mentor and co-mentor come from non-overlapping fields (i.e., a surgeon-scientist and a stem cell biologist), the scholars are required to several required courses, and non-MD scholars are given a two-week clinical immersion in the area of medicine that most closely relates to their area of research.

CIRM-funded training in stem cell laboratory technique

The Center for Human Embryonic Stem Cell Research and Education (hESC) is dedicated to expanding stem cell knowledge among scientists and individuals. Their new, state-of-the-art facility is optimized for stem cell training and they offer several basic and advanced laboratory courses throughout the year.

Demand for these courses has been overwhelming. In the past, courses have been offered free-of-charge through a grant from the California Institute for Regenerative Medicine (CIRM), and therefore could only take students from institutions receiving CIRM funding. Now, however, hESC is advancing plans to offer the course on a fee basis or as part of a partnership with other research institutions, thereby expanding the pool of people who are eligible to take the training. hESC has a facility for iPS cell (induced pluripotent stem cell) derivation from consenting patients. Most courses include some instruction in iPS technology, but laboratories that desire training in deriving human iPS cells can request a special training session.

Courses offered at the training center are:

Basic hESC Biology: This course is one of the central components of our program. It provides the essentials of hESC biology to individuals with little or no previous experience with hESCs. Students will learn the basic techniques required to culture, differentiate and analyze hESCs. They will leave the laboratory with basic protocols, appropriate frozen feeder cell preparations for several months of experiments, and established relationships for further assistance and troubleshooting as they begin their experiments in their own designated hESC laboratory space. [More »](#)

Reprogramming and Somatic Cell Nuclear Transfer (SCNT): This is an advanced technique course that we are offering at the Center. Individuals will learn basic method to work with human embryos and SCNT. We also include instruction in derivation of induced-pluripotent stem cell lines.

Human ES Cell Derivation: In conjunction with basic stem cell culturing technique, we also provide researchers an opportunity to learn how to derive human embryonic stem cell lines. This course is offered through special request.

Human Embryology: This training course will teach students the basic method in handling and growing of the early human embryos, such as in vitro maturation (IVM).

The Siebel Stem Cell Institute

In 2008, Stanford and UC Berkeley, in cooperation with the Seibel Foundation, established the Siebel Stem Cell Institute. By bringing together researchers at UC Berkeley and Stanford, the SSCI enables us to understand the root causes of today's most devastating diseases and translate our discoveries into new therapies.

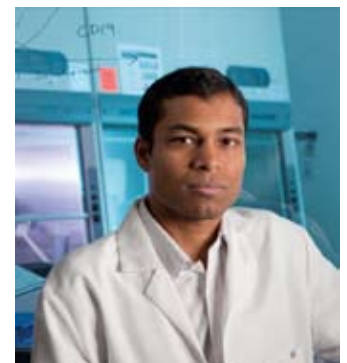
By encouraging collaboration through its visiting scholar program, research fellowships for postdoctoral students, and seed grants for new projects, the Siebel Stem Cell Institute brings leaders in this emerging field together to share their work and leverage the resources of each institution, strengthening both.

The Siebel Scholars at Stanford in 2010

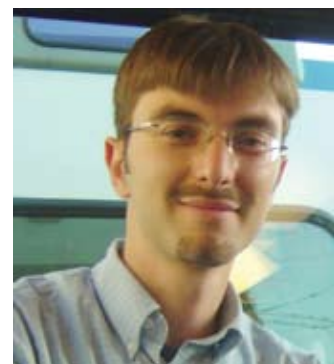
The Siebel Scholars program was established by the Siebel Foundation in 2000 to recognize the most talented students at the world's leading graduate schools of business, computer science, and bioengineering. Each year, 80 exceptional students receive a \$35,000 award during their final year of studies based on outstanding academic performance and leadership.

Established as a private foundation in 1996, the Siebel Foundation is a nonprofit, public benefit corporation. Its mission is to support projects and organizations that work to improve the quality of life, environment, and education of its community members.

Debashis Sahoo, Ph.D., has continued as a Siebel Visiting Scholar at Stanford. Earlier, this computer scientist developed algorithms that use Boolean logic to identify specific genes involved in the development of the blood-forming stem cell into the mature blood cell. He continues to work with Dr. Jun Seita in the Weissman lab to finish a Gene Expression Commons web site, which contains information on the gene expression of each cell in the blood-forming cell lineage, purified prospectively, for both mouse and human cells. With Dr. Charles Chan, they are establishing a parallel site for the stem and progenitor cells in the mouse bone, cartilage, and fat-forming mesenchymal lineages. Dr. Sahoo has now developed an algorithm that takes just milliseconds to come up with the gene names that specify the bladder cancer stem cell and that robustly predict patient survival.



Ivan Dimov, Ph.D., came to Stanford in April 2010 as a Siebel Visiting Scholar, having been a postdoctoral visiting scholar in the lab of Dr. Luke Lee. Dr. Dimov is an assistant professor of biomedical engineering at the University of Valparaiso, Chile, where he is cofounder of the Center for Hospital Technologies. He is also cofounder of the Robotics Research and Development Center at the Technical University Federico Santa Maria in Chile. In collaboration with the Weissman lab, Dr. Dimov has been working on the analysis of cell-surface protein dynamics and also on the design of novel microfluidic methods and tools for single-cell heterogeneity analysis, which is critical for the discovery of new stem cell lineages. Drs. Weissman and Dimov have discovered that, in a one-step process, they are able to discriminate among subpopulations based on gene expression measurements from hundreds to thousands of single cells. Dr. Dimov has also been working with Joseph Wu, M.D., Ph.D., associate professor of medicine (cardiovascular medicine) and of radiology, on developing a new nanoparticle transfection method for reprogramming



Hiroo Ueno, M.D., Ph.D. was a Siebel Visiting Scholar at Stanford through July 2010. He has since returned to Japan as a professor at Kansai Medical University, bringing with him his collaborative experience at Stanford. While at Stanford, Dr. Ueno worked with Dr. Weissman, as well as with Calvin Kuo, M.D., Ph.D., Michael Clarke, M.D., Ph.D., and Mark Krasnow, M.D., Ph.D. Dr. Ueno has continued to employ the method of lineage tracking in mice that he developed while working in the Weissman lab: the multicolored “tetrachimeric mouse” and the multicolored “rainbow mouse.” Tetrachimeric mice are generated by the injection into mouse blastocysts of three kinds of colored embryonic stem cell clones, while rainbow mice employ a mediated multicolor mosaic system. Tetrachimeric mice allow researchers to trace embryonic stem cells as they develop; regions of tissues and organs derived by a single stem cell appear as a single color. Rainbow mice enable any cell to be labeled in its embryonic and fetal stages or in adulthood with a random color by using tissue-specific promoters.

