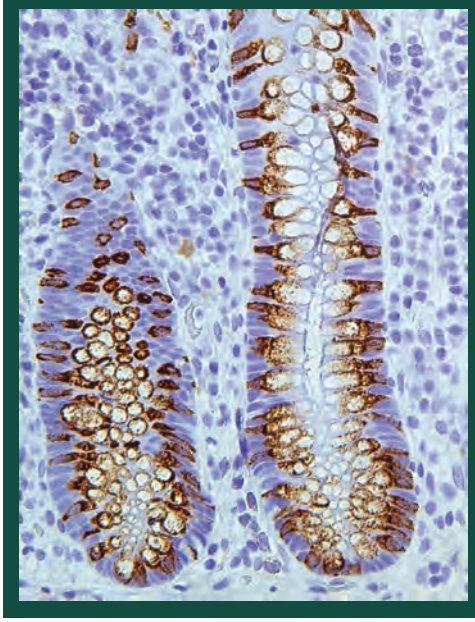
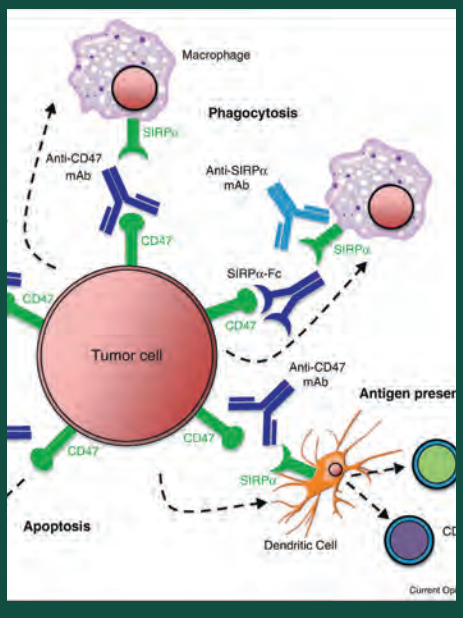
STANFORD
MEDICINE

Institute for Stem Cell Biology
and Regenerative Medicine

2011 Annual Report





2011 Annual Report

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Director's Statement

The institute was established nearly ten years ago, with a vision of building basic and translational stem cell science through collaboration across every area of scientific research. We have succeeded spectacularly, creating a uniquely strong program that is poised to fundamentally change medicine in the next decade.

A number of research initiatives at the institute are rapidly heading toward clinical trials. One very exciting effort concerns CD47, a cell surface protein that protects cancer from the immune system and seems to be found on nearly every kind of cancer. In the coming years, we will be moving forward with preparations for a clinical trial of the anti-CD47 antibody. When this antibody blocks the CD-47 "don't eat me" signal on cancer cells, the body's own immune system attacks the cancer, shrinking large tumors, eliminating small ones, and blocking the metastatic spread of cancer.

Renee Reijo Pera, in conjuction with Stanford bioengineers, has developed a system to monitor the development of blastocysts produced by in-vitro fertilization, so that only the most viable embryos are used for implantation. The system is headed for clinical trials in the United States, but is already in use in the United Kingdom. Phil Beachy has just completed a clinical trial of Intraconozole, a common antifungal agent that inhibits the hedgehog pathway active in basal cell carcinoma, and is moving toward a clinical trial of that drug combined with arsenic to make the anti-hedgehog activity more potent. Marius Wernig, in association with Alfred Lane and Anthony Oro, is moving toward a clinical trial of a stem cell treatment for epidermolysis bullosa, a skin disease that in its most extreme form can cause blistering so severe that patients get painful blisters from the lightest touch and are not likely to live past childhood.

In the last year we have hosted two visiting professors who are themselves leaders of stem cell institutes, Hiro Nakauchi and Roger Pedersen. Both of these researchers are working on creating tissue-specific stem cells from pluripotent stem cells.

Central to our vision for the near future is the establishment of the Stanford Stem Cell Therapy Center. This center, which will be ensconced in the Stanford Hospital, will enable the clinical-grade purification of stem cells that can be used in human therapies and clinical trials. In animal models and limited clinical trials, purified blood stem cells have been shown to be effective in treating severe combined immune deficiency

(SCID, the so-called “bubble boy” disease) as well as autoimmune disorders such as multiple sclerosis, lupus, type 1 diabetes, and so on.

As we move stem cell biology from discovery to regenerative medicine that can be used clinically, many groups are focusing on making adult stem cells from pluripotent cells, especially those pluripotent cells that are created from a defined patient through reprogramming.

The presence of the Stem Cell Therapy Center will also allow us to conduct a much larger clinical trial of a promising therapy using high-dose chemotherapy and purified blood stem cell rescue for stage-4 breast cancer. The original small trial was conducted over a dozen years ago, and a recent follow up revealed that one third of breast cancer patients taking part in the Stanford trial were still alive, a huge improvement over the 4 to 7 percent of women who survive this long with standard therapy.

The future of organ transplantation is also closely tied to stem cell therapies. Researchers at Stanford have shown that when organ transplants are accompanied by transplantation of blood stem cells from the organ donor, tissue tolerance for the donated organ is induced. This leads to a much higher success rate for the transplant operation and frees patients from a lifelong need for anti-rejection drugs. Researchers at Stanford are also working on antibody-based techniques that clear a spot in the host’s stem cell niche. This allows a much gentler method for giving blood stem cell transplantations than the existing high-dose regimens of chemotherapy.

Lastly, the institute is preparing a bright future for stem cell research by educating the next generation of stem cell scientists. The ISCBRM has begun the first PhD program in the nation devoted solely to stem cell biology and regenerative medicine. The curriculum includes clinical rounds so that students become well aware of the needs of patients and physicians in the clinic, making this unique among PhD programs in that it is explicitly oriented toward translational science. The first students begin their studies in the Fall of 2012.

On these and many other fronts described in these pages, physician scientists, scientific physicians, engineers, computer scientists and many others at Stanford will collaborate to move research projects out of the laboratory and shepherd them through early clinical trials. Only at Stanford are there such close ties between the institute, the School of Medicine and the School of Engineering, providing an environment in which we can turn stem cell science into truly regenerative stem cell medicine.

Irving L. Weissman
Director

Teacher Ellyn Perez became the first person cured of advanced metastatic breast cancer using purified stem cells.

ISCBRM plans to launch a Stem Cell Therapy Center

In the past, Stanford researchers have played a key role in understanding stem cell biology and have taken the first critical steps toward moving those advances into the clinic. In the 1980s, for instance, Institute Director Irv Weissman isolated the first human hematopoietic (blood) stem cell. A decade later, Stanford was conducting the only clinical trial in the world using purified blood stem cells and high-dose chemotherapy to treat women with stage-4 breast cancer.

The institute is now preparing to take the next major step in the translation from stem cell science to regenerative medicine. In cooperation with Stanford Hospital, the ISCBRM will be establishing a Stem Cell Therapy Center at Stanford University, a first-of-its-kind facility where tissue-specific stem cells can be purified at an academic medical center in sterile, clinically appropriate conditions that make them suitable for human therapeutic use.

A stem cell therapy facility will open the door to treating people with a broad range of deadly diseases that are resistant to current therapies. Stanford stem cell scientists have conducted many proof-of-principle experiments in mice demonstrating unequivocally that a one-time treatment with purified stem cells can cure some chronic disorders for life. Diseases that initially can be treated this way are type 1 diabetes, multiple sclerosis, lupus, severe combined immune deficiency (SCID--also called the “bubble-boy disease”), sickle cell anemia, and Mediterranean anemia (thallasemia).

A one-time treatment with purified stem cells can cure some chronic disorders for life.

The Stem Cell Therapy Center will also facilitate the resumption of clinical trials to treat cancer patients with purified blood stem cell transplants after high dose chemotherapy. In the original Stanford trial, women with advanced, metastatic breast cancer were treated with very high doses of toxic chemotherapeutic agents in the hope that these high doses

would be more effective at killing cancer stem cells than standard chemotherapy. This aggressive chemotherapy has the drawback of killing blood-forming stem cells in addition to the cancer, so the blood-forming system has to be repopulated through a stem cell transplant.

A small group of advanced breast cancer patients were treated in the first clinical trial over fifteen years ago. Antonia Mueller, a postdoctoral fellow working with Dr. Judy Shizuru, tracked down the fate of those Stanford patients 12-14 years later. Of the women whose cancers showed sensitivity to chemotherapy (women who faced less than 5 percent chance of long-term survival with standard treatment) over 30 percent are still alive more than a dozen years later, most with no signs of cancer. The Stanford Stem Cell Therapy Center will play a key role in conducting a much larger clinical trial of this promising therapy.

We are now about to enter a new era in which truly regenerative medicine will be a standard part of medical practice

Transplantation of the heart, lungs, liver, kidneys, skin and many other organs and tissues has become common throughout the world. But failure of the procedure is most often the result of an immune system attack on the transplanted organ. Even when the operation is successful, transplant recipients have to take drugs for the rest of their lives to keep the transplanted organ from being rejected. But if the organ transplant is accompanied by a transplant of blood stem cells from the organ donor, tolerance to the new organ is induced, making transplantation operations more successful and freeing patients from lifelong bondage to anti-rejection drugs.

We are now about to enter a new era in which truly regenerative medicine will be a standard part of medical practice. Stem cell researchers at Stanford and elsewhere will continue to discover and purify stem cells for the heart, lungs, vascular system, skin and other important tissues. The Stem Cell Therapy Center at Stanford University will speed the day when treatments for the vast majority of diseases and conditions will include some form of therapy with purified human stem cells.

Stem cells will be purified using clinical grade, fluorescence-activated cell sorting (FACS) machines.

CIRM Disease Teams

The California Institute for Regenerative Medicine (CIRM) has awarded large grants to select groups of researchers to accelerate advances on the treatment of specific diseases. These disease teams are designed in such a way that each elite, interdisciplinary team works together to use stem cell-based therapies to make progress on treating these disease within a four-year timeframe.

Stanford School of Medicine is host to five of these elite teams, four of which involve researchers within the Institute for Stem Cell Biology and Regenerative Medicine.

CD47 Disease Team

CD47 is a protein found on the surface of some cells and protects cells from being ingested by the immune system's macrophage cells. This "don't eat me" signal to the macrophage is found on nearly every type of cancer, and is believed to be responsible for protecting cancer stem cells from attack by the immune system. Blocking the CD47 signal with anti-CD47 antibodies has been shown to shrink or eliminate human cancers in mice.

The CIRM-funded CD47 Disease Team Program is focused on producing new therapeutic candidates to prolong remission and potentially cure highly lethal cancers for which patients otherwise have few treatment options. The team's strategy is to develop an antibody that will eliminate the cancer stem cells that are the source of the disease, and are also responsible for the recurrence that can occur months to years following the remission achieved with initial clinical treatment. The cancer stem cells are a small part of the total cancer cell burden, and they appear to be resistant to the standard treatments of chemotherapy and radiation therapy-–therefore new therapeutic approaches are needed to eliminate them.

Over the last year, the team has continued to develop a clinical-grade antibody that will eliminate the cancer stem cells in Acute Myelogenous Leukemia (AML). The team has developed an antibody that binds to CD47 on human leukemia cells. This antibody causes human leukemia cells to be eaten and destroyed by healthy human white blood cells when tested in cell culture experiments, and can eliminate leukemia growing in mice injected with AML cells obtained from patients. Their pre-clinical development has included many steps:

• 'Humanization' of the antibody: The antibody has been optimized so that it looks like a normal human protein that the patient's immune system will not eliminate because it appears 'foreign' to them.

• Large scale production of the antibody: The team has made arrangements for the production of sufficient quantities of the antibody to complete the laboratory experiments and to move on to clinical safety trials with patients

• Pre-clinical safety studies: The antibody has been tested in animals to ensure it does not cause serious limiting damage to any of the normal healthy tissues. Thus far, these assessments have revealed no major toxicity hurdles to further clinical development.

> The CD47 protein is found on nearly all types of cancer

During the run-up to the trial, the CD47 Disease Team (led by Irv Weissman, MD and Ravi Majeti, MD, PhD) found that all human cancers tested are CD47 positive and susceptible to anti-CD47 antibody therapy (see page 16). In July 2012, CIRM approved extending future clinical trials to all human cancers.

Most recently, the team has initiated discussions with the FDA and hopes to start clinical trials in late 2013 or early 2014.

Skin Disease Team

Genetic skin diseases constitute a diverse group of several hundred diseases that affect up to two percent of the population. Common diseases include psoriasis and difficulty with wound healing. Patients with one genetic disease, dystrophic epidermolysis bullosa (EB), lack a collagen gene and suffer from debilitating blistering. This extremely painful blistering starts soon after birth and leads to chronic wounds and scarring that can be lethal by young adulthood. The disease is devastating and, despite all researchers' efforts, current therapy for EB is limited to caring for the wounds after blistering has occurred.

The world's first iPS cell-based clinical trial is on the horizon, and it will be at Stanford

The CIRM funded skin disease team is composed of Marius Wernig, MD, assistant professor of pathology, and his colleagues Anthony Oro, MD, PhD, associate professor of dermatology, and Alfred Lane, MD, professor of dermatology. Their goal is to grow EB patients' own skin cells in a culture dish, alter them so that they can make normal collagen again, and then graft them back onto the patients' skin. This approach includes a number of complicated cell culture steps, including initially the generation of induced pluripotent stem (iPS) cells from the skin cells of the individual patient. These iPS cells share with embryonic stem cells the characteristic that they can give rise to all the cells in the body. Their great advantage is that genetic mutations can be fixed in this state.

The team has already shown (i) that iPS cells can be generated from patients affected with this particular skin disease, (ii) that the genetic problem causing the disease can be corrected, (iii) that these corrected iPS cells can be differentiated into skin cells that look just like cells directly taken from human skin and (iv) that these iPS cell-derived skin cells can form human skin when transplanted on the back of a mouse. Thus, all the critical steps that are necessary for the development of this cell therapy are worked out. From a scientific point of view, therefore, there are no longer any principle obstacles to clinical application. Consequently, the project is moving now from the discovery to the application mode.

The next critical step is to translate what has been done so far in a research lab into a tightly controlled, FDA-approved manufacturing process. The team expects this process to be at least as difficult and important as the research phase. Safety will always be of the utmost importance in these trials, and the team is now discussing important safety criteria. Once the group and the FDA have come to a consensus on those criteria and the iPS cell-derived skin cells pass those tests, a Phase I clinical trial will be initiated. Thus, the world's first iPS cell-based clinical trial is on the horizon and it will be performed at Stanford.

The researchers' ability to reprogram and replace diseased skin would allow them to use this procedure to develop therapeutic reprogramming approaches for a variety of both common and life-threatening skin diseases. Moreover, genetically corrected pluripotent iPS cells could form the basis of future systemic therapies to treat common genetic disorders of organs other than the skin.

Blood Stem Cell Transplant Disease Team

Successful stem cell therapy requires the replacement of diseased or dysfunctional stem cells with healthy ones. These healthy stem cells can come from either a donor or can be stem cells that are modified by gene therapy techniques. One important step in this process of repair and replacement is to eliminate the existing diseased cells so that physical space is created for the healthy ones, and competition for environmental factors that nurture and support the stem cells are removed.

The oldest and most commonly used form of stem cell therapy is bone marrow transplantation (BMT). Thousands of patients undergo BMT yearly to treat cancers or disorders of blood formation. Bone marrow contains many different kind of cells, only a minority are the blood-forming stem cells. These stem cells are critically important as only stem cells can permanently generate new blood and immune cells. In a BMT, stem cells from a donor replace the recipient's diseased stem cells. Currently, the only way to eliminate the patient's own blood forming stem cells is to treat the recipient to accept donor cells with toxic agents such as radiation or chemotherapy.

The blood stem cell disease team will focus on developing a gentler, safer and more effective method for blood stem cell transplantation. The method involves using anti-CD117 antibodies to clear a space in the blood stem cell niche so that the body will accept donor hematopoietic stem cells. The disease team initially will focus on developing the technique for use in curing severe combined immunodeficiency (SCID). Children with SCID suffer a genetic deficiency that impairs the activity of T and B cells.

The only cure for the condition is bone marrow transplantation, but SCID children are not well equipped to deal with the rigors of

Judy Shizuru, MD and Irving Weissman, MD advocate before the CIRM Independent Citizens' Oversight Committee in favor of funding for the blood stem cell transplant disease team.

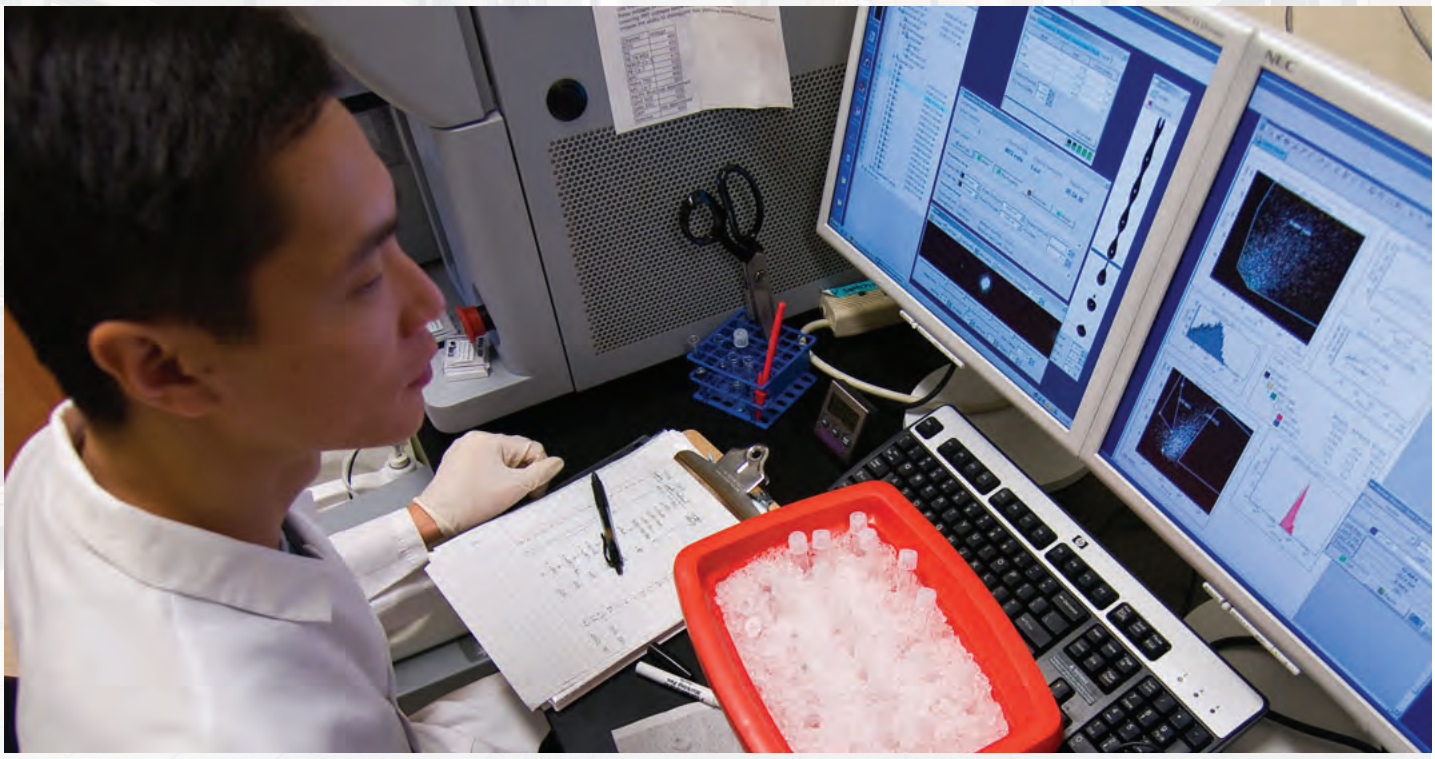
chemotherapy and transplantation. An antibody-based approach to depleting blood stem cells, followed by transplantation with a donor's purified blood stem cells, may offer a safer option.

A gentler method for transplanting blood stem cells could lead to cures for many diseases as well as improvement in organ transplantion and stem cell therapy

A successful therapy based on this model would open the door to treating a wide range of other diseases. Autoimmune disease such as lupus, multiple sclerosis, type 1 diabetes and others could be cured with a one-time treatment that depletes a patient's own blood and immune cell population and replaces them with donor stem cells.

The greatest causes of organ transplant failure and subsequent health problems are immune attacks on the transplanted organ and the effects of drugs that suppress that attack. So in the future every organ transplant might be accompanied by a blood stem cell transplant that would induce immune tolerance to the transplanted organ, freeing patients of a lifelong need to take immunosuppressant drugs.

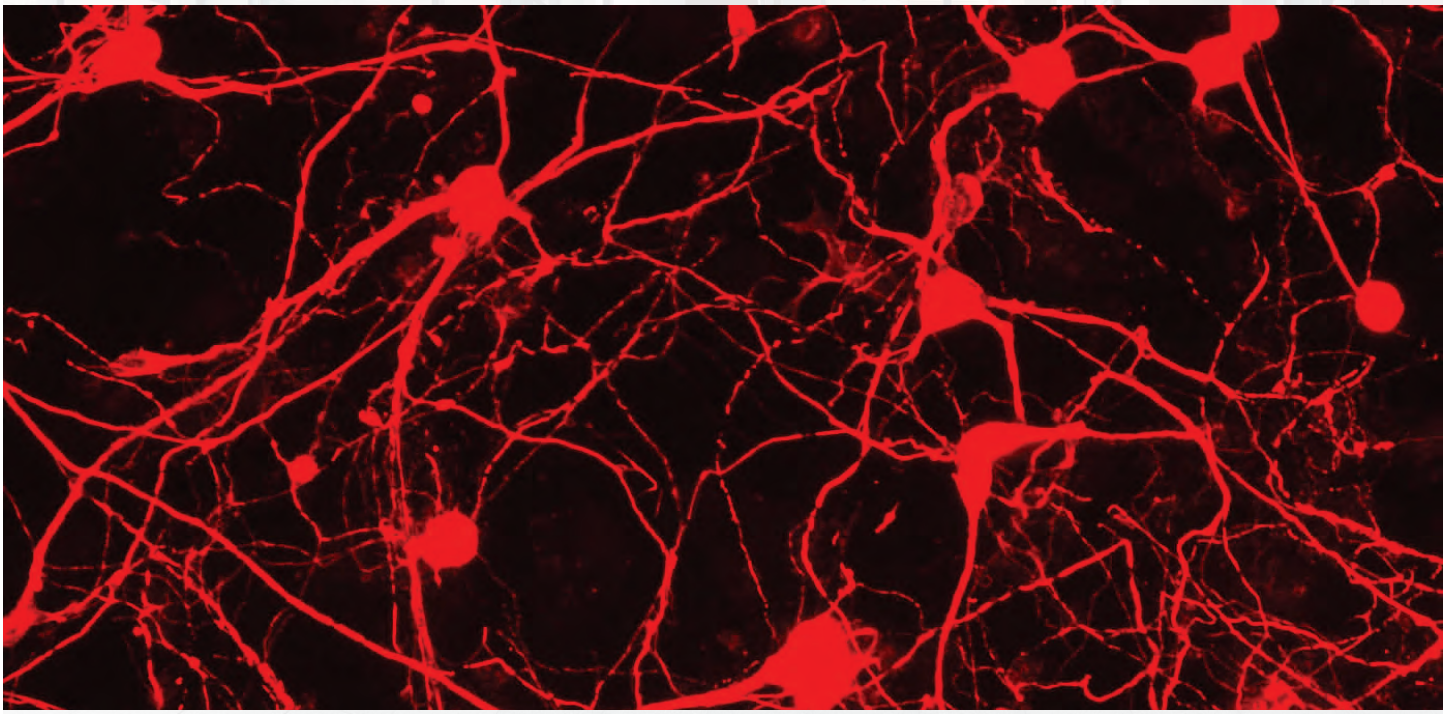
If it turns out that therapies with stem cells or iPS cells are vulnerable to rejection by the immune system, as is reported by some researchers, this therapy may be what's needed to induce immune tolerance to those cells, making regenerative medicine possible in the future.



Blood stem cell purification is done using fluorescence activated cell sorting (FACS).

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 genetic 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, this work may also reveal paths for creating tissue and organ-specific stem cells, which may then be used to heal those tissues and organs.



Cultured neurons that have been created by direct transformation from fibroblasts in the Wernig Lab

Research Highlights:

Discovery may eliminate a potentially lethal side effect of stem cell therapy

The virtue of embryonic stem cells is that they have the potential to become any sort of tissue in the body, but this also turns out to be a problem. Within any batch of cultured cells remain those that are still pluripotent and can become the nucleus for deadly teratomas. Researchers in the Weissman laboratory have discovered the defining features of these teratogenic cells and developed antibodies that can identify and remove them from cell cultures. The ability to remove teratogenic cells eliminates one of the biggest roadblocks to moving stem cell therapies from the research lab into the clinic.

The Center for Human Embryonic Stem Cell Research and Education

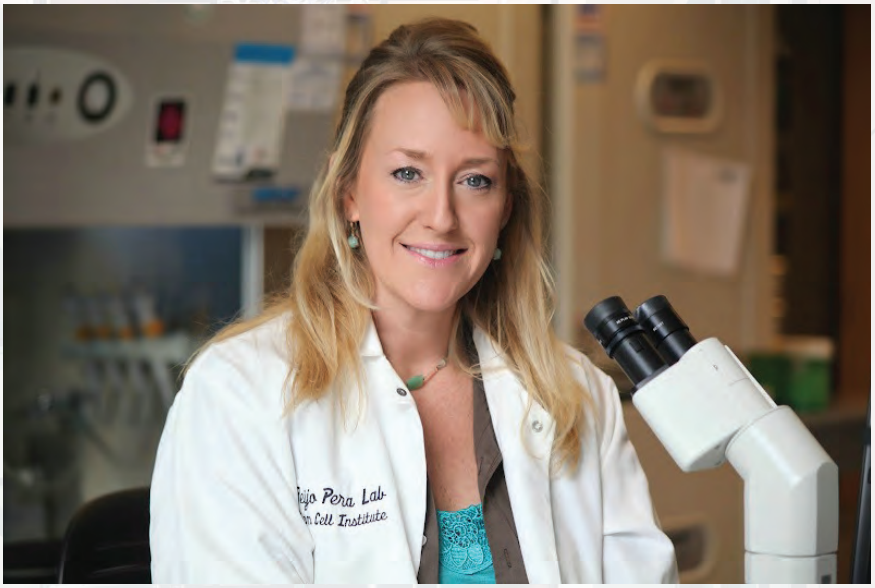
The Center for Human Embryonic Stem Cell Research and Education has become a powerful presence in the world of embryonic research because of its focus on human development. Although researchers around the world study embryonic stem cells from mice or other organisms, human embryonic stem cells can behave 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.

Renee Reijo Pera, PhD, Director of the Center for Human Embryonic Stem Cell Research and Education

Stanford Researchers Find Genetic Markers of Fertility in Women

Researchers at the Stanford Institute for Stem Cell Biology and Regenerative Medicine have discovered genetic markers that may ultimately allow women to track and predict declining fertility. Ultimately, this study and further research may let individual women know in advance the approximate age when their fertility will decline, allowing them to plan accordingly.

"Many women now are delaying childbirth until their mid to late 30s, which is getting very near the edge of the common fertility window," says Sonya Schuh-Huerta, PhD. Some of these women are destined to have diminished fertility by the time they try to have children, but they won't know that in advance, she says.



Sonya Schuh-Huerta, PhD

Testing for the number of maturing eggs in the ovary and levels of reproductive hormones can be a good indication of fertility, but women tend not to get these tests until they are already experiencing difficulties with conceiving, Schuh-Huerta says. "Ultimately, a test for specific genetic markers would be easier and could give them more information and more power to make reproductive decisions," she says.

The age of onset of menopause is highly determined by genetics, a fact that many women don't know, says senior author Renee Reijo Pera, PhD. She and her colleagues performed a genome-wide association study (GWAS) and found genes that were associated with early declines or rises in reproductive hormones in two very distinct populations of women.

The researchers hope that the new gene markers will also help clinicians better gauge fertility and interpret the hormonal tests.

Manganese and repeated MRI help monitor and kill teratogenic cells in embryonic stem cell grafts

Although human embryonic stem cells (hESC) have tremendous therapeutic potential, teratoma formation has deterred translation into clinical therapies. Stanford researchers found that teratogenic cells in an embryonic stem cell-derived graft would take up manganese more than other implanted stem cells. They also discovered that repeated MRI scanning of the graft could allow the researchers to both image the teratogenic cells and kill them.

Study finds that iPS cells equal embryonic stem cells in modeling human disease

Institute researchers showed that iPS cells, which are viewed as a possible alternative to using human embryonic stem cells, can mirror the defining defects of a genetic condition — in this instance, Marfan syndrome — as well as embryonic stem cells can. An immediate implication is that iPS cells could be used to examine the molecular aspects of Marfan syndrome, or other diseases, on a personalized basis. Embryonic stem cells, on the other hand, can't do this because their genetic contents are those of the donated embryo, not the patient's.

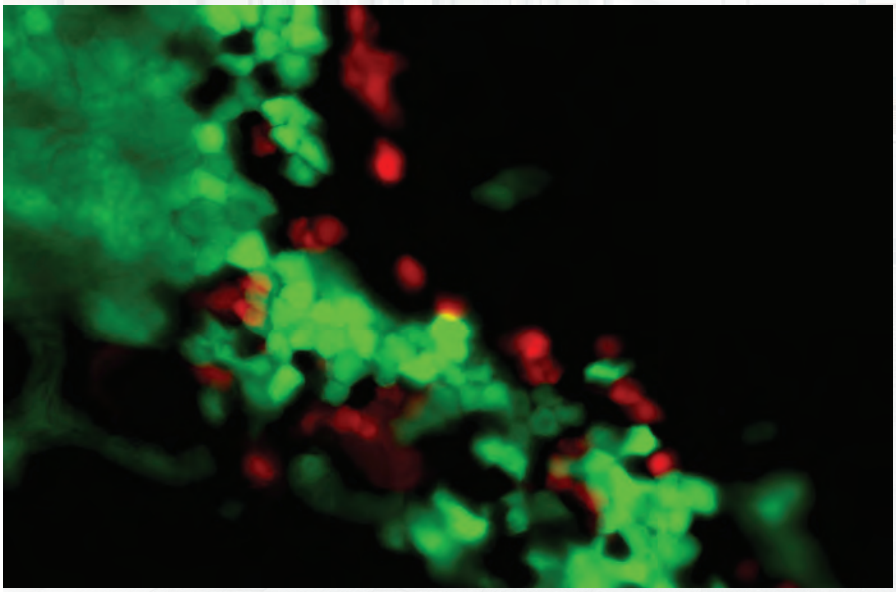
This proof-of-principle for the utility of induced pluripotent stem cells also has more universal significance, as it advances the credibility of using iPS cells in modeling a broad range of human diseases. These cells, unlike embryonic stem cells, are easily obtained from virtually anyone and harbor a genetic background identical to the patient from which they were derived. Moreover, they carry none of the ethical controversy associated with the necessity of destroying embryos.

In this study, both iPS cells and embryonic stem cells carrying a mutation that causes Marfan syndrome showed impaired ability to form bone and all too readily formed cartilage. These aberrations mirror the most prominent clinical manifestation of the disease.

Induced Pluripotentent 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 via 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.

Scientists turn skin cells into neural precursors, bypassing stem-cell stage



Researchers in the Wernig lab discovered that mouse skin cells can be converted directly into cells that become the three main parts of the nervous system. The finding is an extension of a previous study by the Wernig lab showing that mouse and human skin cells can be directly converted into functional neurons.

This result raises the possibility that embryonic stem and iPS cells could be replaced by this more direct way of generating specific types of cells for therapy or research.

This new study was a substantial advance over the previous work in that

it transforms the skin cells into neural precursor cells, as opposed to neurons. While neural precursor cells can differentiate into neurons, they can also become the two other main cell types in the nervous system: astrocytes and oligodendrocytes. In addition to their greater versatility, the newly derived neural precursor cells offer another advantage over neurons because they can be cultivated to large numbers in the laboratory — a feature critical for their long-term usefulness in transplantation or drug screening. Not only do the cells appear functional in the laboratory, they also seem to be able to integrate appropriately in an animal model.

Marius Wernig, MD, PhD

"In addition to direct therapeutic application, these cells may be very useful to study human diseases in a laboratory dish or even following transplantation into a developing rodent brain," Wernig says.

Study of stem cell diseases advanced by new technique

A rare genetic disease called dyskeratosis congenita, which is caused by the rapid shortening of telomeres (protective caps on the ends of chromosomes), can be mimicked through the study of undifferentiated, induced pluripotent stem cells, researchers at the institute discovered. Although dyskeratosis affects only about one in a million people, the scientists' findings could greatly facilitate research into this and other diseases caused by stem cell malfunctions, including some bone marrow failure syndromes and, perhaps, pulmonary fibrosis.

The research, which used iPS cells created from the cells of patients with dyskeratosis, explains why sufferers experience a wide variety in the types and severity of symptoms, ranging from abnormal skin pigmentation and nail growth to lung scarring, bone marrow failure and cancer. The key lies in the activity of telomerase, an enzyme critical to aging and cell renewal.

"We were very surprised to find such a clear correlation between the quantity of functional telomerase, the severity of the cellular defect and the severity of the patient's clinical symptoms," said associate professor of medicine Steven Artandi, MD, PhD, who collaborated on the study with institute researcher Renee Reijo Pera, PhD. "Our work suggests that, in patients with dyskeratosis congenita, tissue stem cells are losing their ability to self-renew throughout the body. This is a new, unifying way to think about this disease, and it has important implications for many other conditions."

Cancer Stem Cells

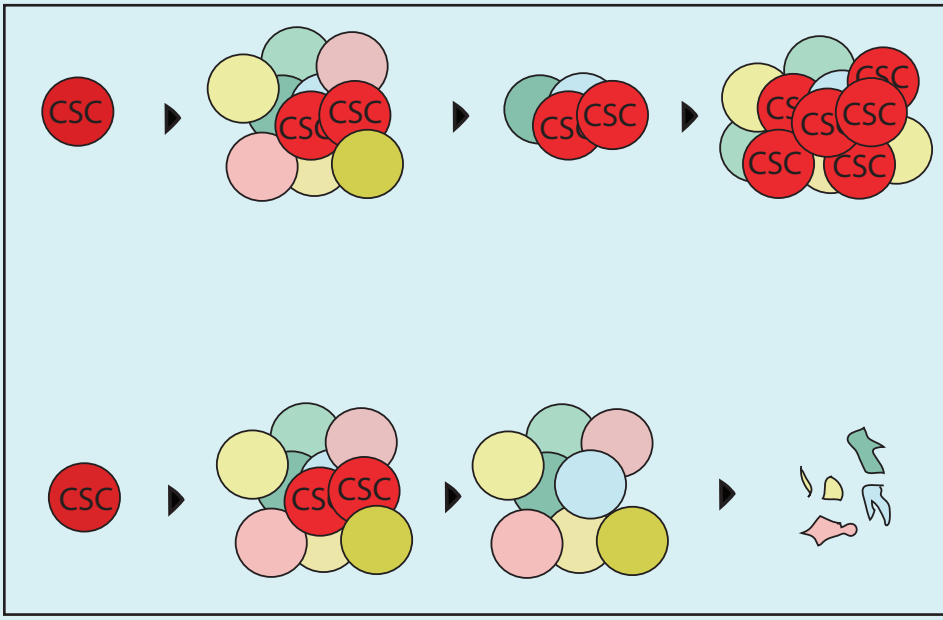
Attacking Cancer at the Root

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 vulnerabilities that can be exploited in targeted treatments.

The cancer stem cell theory proposes that all cancers contain cancer stem cells, which 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 are often a minority of the cells in a cancer.

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.

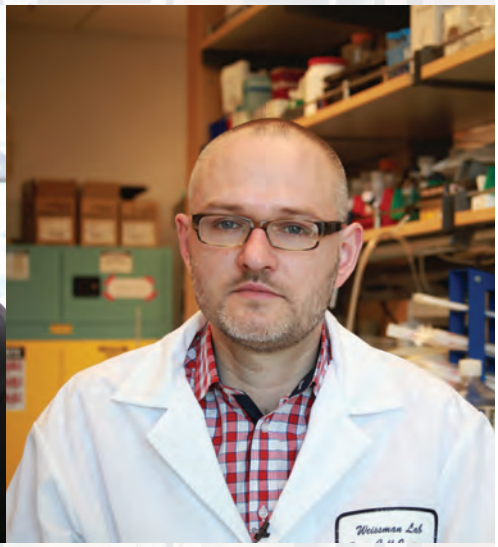
This year, researchers made significant progress in using antibodies to a marker that protects cancer cells in order to help the immune system attack and destroy those cells. They also developed techniques that help us identify, track and understand cancer stem cells in specific cancers.



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.

Research Highlights:

Single antibody shrinks variety of human tumors transplanted into mice, study shows



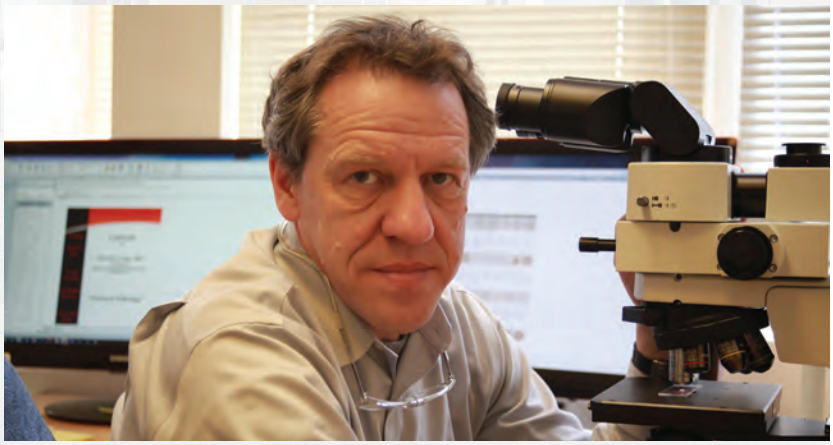
Stephen Willingham, PhD, and Jens Peter Volkmer, MD

During the past year, researchers at the institute extended dramatic findings about the use of use of anti-CD47 antibodies as an anti-cancer therapy. Previously, scientists had discovered that the cell surface marker CD47 acts as a "don't eat me" signal to roving macrophage cells, and that high levels of CD47 are found on most leukemia lymphoma cells. The researchers also discovered that blocking the CD47 signal with custom antibodies would lead macrophage cells to eat leukemia cells in mice. This macrophage-mediated cancer treatment was extended to lymphomas by combining anti-CD47 antibodies and rituximab, an antibody that reinforces "eat me" signals that are present on lymphoma cells.

In further experiments done this year, these promising results were extended from blood cancers to solid tumors. Human tumors transplanted into laboratory mice disappeared or shrank when scientists treated the animals with the anti-CD47 antibody. The scientists achieved these findings with human breast, ovarian, colon, bladder, brain, liver and prostate cancer samples.

"Blocking this 'don't-eat-me' signal inhibits the growth in mice of nearly every human cancer we tested, with minimal toxicity," said institute director Irv Weissman. "This shows conclusively that this protein, CD47, is a legitimate and promising target for human cancer therapy." Two researchers in the Weissman lab, Stephen Willingham, PhD, and Jens Peter Volkmer, MD, were first authors on the published research.

The antibody treatment also significantly inhibited the ability of the tumors to metastasize throughout the animals' bodies. In a collaboration with Badreddin Edris, PhD and Matt van de Rijn, MD, a rapidly spreading type of cancer (leiomyosarcoma) had all of its metasteses removed by anti-CD47 treatment after the cancer cells spread. It is the first antibody treatment shown to be broadly effective against a variety of human solid tumors.



Matt van de Rijn, MD

The dramatic response — including some overt cures in the laboratory animals — has

the investigators eager to begin phase 1 and phase 2 human clinical trials within the next two years. The California Institute for Regenerative Medicine (CIRM) has provided a $20 million grant to help initiate these clinical trials.

Computer algorithm used to identify bladder cancer marker

Researchers at the Stanford University School of Medicine have used an innovative mathematical technique to find markers that effectively predict how deadly a cancer will be. The discovery, which in this case concerned bladder cancer, could lead to faster, less expensive and more accurate analysis of cancer risk and better treatment of the disease.

This is the first study in which a special, Stanford-designed computer algorithm was used to identify a clinically prognostic marker from public databases. The search tool was introduced in a paper published two years ago and established its effectiveness in identifying markers in mice.

Bladder cancer is the sixth most common malignancy and is responsible for about 15,000 deaths per year in the United States. Currently, the severity and aggressiveness of bladder cancer is gauged by a pathologist, who inspects a sample of the cancer tissue in the laboratory. This approach requires time and the expertise of a specialist. “This approach is very subjective and can result in conflicting reports from expert pathologists,” said Debashis Sahoo, PhD, a Thomas and Stacy Siebel Fellow in the institute and one of three lead authors on the paper. The new research offers the promise of an easy, antibody-based test that can be used by someone with little training to quickly determine whether a bladder cancer is of the most dangerous type.

Allowing clinicians to evaluate the risk of individual tumors based on their molecular characteristics will have a profound impact on the health care of bladder cancer patients, the researchers said. “Currently there is no way to predict if a patient has the less- or more-aggressive subtype of bladder cancer early on,” said Jens Peter Volkmer, MD, another first author of the paper and a postdoctoral scholar at Stanford. “This technique might be used to identify the patients with the more-aggressive subtype before the cancer becomes invasive or metastatic.”

Advanced technologies give high-resolution ‘snapshot’ of cancer tissues

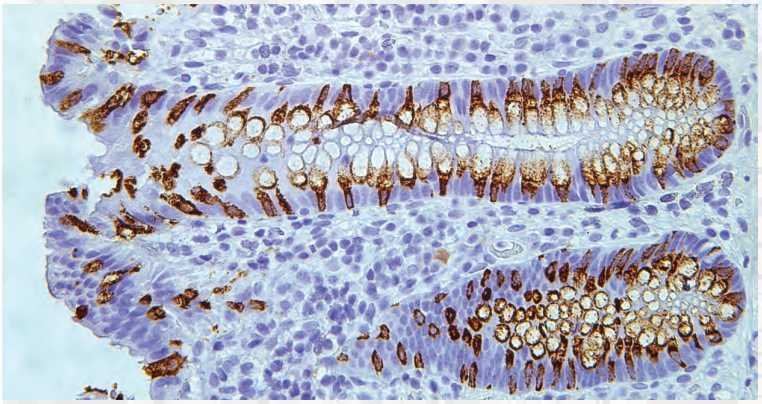
Stanford researchers have melded tools and technologies from engineering, computer science and stem cell biology to analyze hundreds of individual cancer cells and draw the most accurate portrait yet of the cellular composition of human colon cancer tissues.

In doing so, they have shown that the development of cancer is a kind of caricature of normal tissue development, and have discovered markers that allow them to gauge more accurately how dangerous a cancer is likely to be. They hope the work will lead to better and more targeted cancer therapies.

Debashis Sahoo, PhD

In tumor tissues, not all cancer cells are created equal. Solid tumors usually contain many kinds of cancer cells, each of which might be more or less dangerous, and may vary in how they respond to various anti-cancer therapies.

A team led by Stephen Quake, PhD, and Michael Clarke, MD, used the single-cell microfluidic technology



Colonic Crypts

invented in the Quake laboratory to analyze the individual gene-expression profile of hundreds of single colon cancer cells, which they then grouped into different subtypes.
Using these technologies to analyze the gene-expression patterns of single cells, one by one, allows the researchers to dissect their different identities and clarify the physiology of complex tissue systems.

"In a single experiment, we can now take a 'snapshot' of the cell composition of a specific tissue, visualize its different cellular subsets and easily discover novel markers to define them," said research associate Tomer Kalisky, PhD.

Aging stem cells may explain higher prevalence of leukemia, infections among elderly, study shows
Human stem cells aren't immune to the aging process, according to scientists at the Stanford University School of Medicine. The researchers studied hematopoietic stem cells, which create the cells that comprise the blood and immune system. Understanding when and how these stem cells begin to falter as the years pass may explain why some diseases, such as acute myeloid leukemia, increase in prevalence with age, and also why elderly people tend to be more vulnerable to infections such as colds and the flu.
"We know that immune system function seems to decline with increasing age," said Wendy Pang, MD, commenting on work she did as an MSTP student under Irv Weissman, MD and Stanley Schreier, MD. "This is the first study comparing the function and gene expression profiles of young and old purified, human hematopoietic stem cells, and it tells us that these clinical changes can be traced back to stem cell function."
Specifically, the researchers found that hematopoietic stem cells from healthy people over age 65 make fewer lymphocytes — cells responsible for mounting an immune response to viruses and bacteria — than stem cells from healthy people between ages 20 and 35. Instead, elderly hematopoietic stem cells, or HSCs, have a tendency to be biased in their production of another type of white blood cell called a myeloid cell. This bias may also explain why older people are more likely than younger people to develop myeloid malignancies.

Survival of stage-4 breast cancer patients improves with stem cell treatment, study finds
A new long-term study of women with stage-4 breast cancer at the Stanford University School of Medicine is likely to revive a decade-old debate about high-dose chemotherapy as a treatment option. Specifically, researchers found that a greater proportion of patients who received the aggressive treatment over a dozen years ago, followed by a rescue with their own, specially purified blood stem cells that had been purged of cancer, survived compared with those who were rescued with unmanipulated blood grafts.
The study, although small, is the first to analyze the long-term outcomes of women who received their own

(autologous) stem cells that had undergone this purification process. While high-dose chemotherapy followed by autologous blood stem cell transplantation was largely discarded at the end of the 1990s (interim analyses of several then-ongoing phase-3 clinical trials suggested it produced no better outcomes than other forms of treatment) women in this study received blood stem cells that had been prepared very differently.
"Most people in the oncology community feel that this issue is a done deal, that high-dose chemotherapy does not work for patients with breast cancer," said associate professor of medicine, Judith Shizuru, MD, PhD. "But our study suggests that the high-dose therapy strategy can be modified to include the use of cancer-free purified blood stem cells to yield better overall outcomes in women with advanced breast cancer."

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

A pediatric brain tumor that causes gruesome suffering is finally yielding its secrets. For the first time, institute researcher Michelle Monje, MD, PhD has cultured human cells from this cancer, diffuse intrinsic pontine glioma (DIPG), and have succeeded in transplanting the cancer into the brains of immune deficient mice 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.

Monje has teamed with institute researcher Philip Beachy, PhD, to focus on a specific molecular signaling pathway (known as the Hedgehog pathway) that they thought might be driving development of DIPG cells. The Hedgehog pathway has already been shown to play a role in the growth of several other kinds of brain tumor. 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.

Philip Beachy, PhD

Michelle Monje, MD, PhD

Tissue-Specific (Adult) Stem Cells
Studying the Framework of Future Therapies

Embryonic stem cells are able to become any kind of cell in the body. As an organism grows, however, stem cells become more specialized. At that point they become what is often called “adult” stem cells, able to become only specific kinds of tissue. For most of our lives, 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 are more mature than embryonic stem cells, even though they are also present in children.
Learning how these tissue-specific stem cells operate will help us bolster our natural regenerative abilities. Many of the signs and symptoms of aging are mostly due to the declining ability of stem cells to renew tissues and organs.

Research Highlights:

Discovery of niche cells that support and regulate colon stem cells
The lining of the colon, the colonic epithelium, is completely regenerated every few days throughout our lifetimes. Stem cells drive this process, but they must be tightly controlled and regulated or they may grow too quickly and turn into colonic polyps or colon cancer. On the other hand, if they grow too slowly and their proliferation fails to keep up with the turnover of the tissue, an ulcer may result. So the colon has developed a complex molecular network that regulates stem cell growth through a microenvironment called the “stem cell niche.” Stanford researchers used multicolor flow cytometry and single-cell gene expression analysis (both technologies that were invented and developed at Stanford) to find a population of niche cells that support and regulate colon stem cells. Studying these niche cells (which have the surface marker cKit/CD117) will help us understand the regulation of colonic stem cells and will ultimately lead to a better understanding of many diseases of the colon, such as colon cancer or inflammatory bowel disease.

Piero Dalerba, PhD

Researchers identify mechanism for repairing bladder infection damage; also find possible bladder stem cell

The bladder is a supple, muscular organ with a well-defined task: store urine and release it at an appropriate time. But when the bladder becomes infected, it launches a massive, scorched-earth attack, sloughing off the innermost layer of cells to keep invading bacteria from latching onto and burrowing into its inner lining.

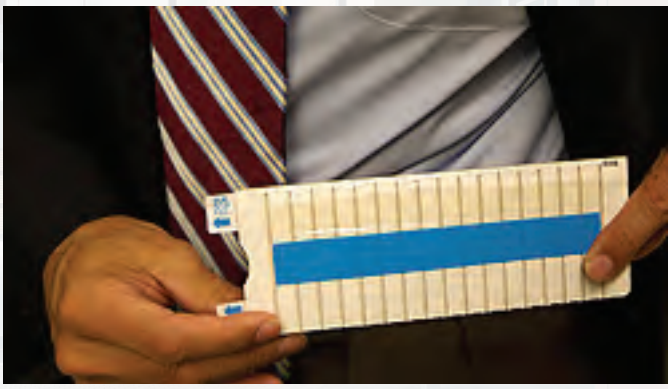
Now scientists at the institute have identified the key molecular pathways that form a control circuit involved in kick-starting cell division in the bladder to repair the damage. They've also pinpointed what appear to be bladder stem cells critical to the repair. The research could lead to new ways to treat bladder infections and other, more deadly, problems.

Philip Beachy, PhD

"We suspect that this pathway of regeneration might be important in cancer development and metastasis in the bladder and other organs, like the prostate," said developmental cell biologist Philip Beachy, PhD. The feedback loop regulating tissue repair involves the proteins wnt and sonic hedgehog, which are also thought to be involved in the development of some cancers. The research is consistent with a model in which cancer can occur when the mechanisms that cells use to repair tissue are turned on too strongly or for too long.

New device to reduce surgical scarring

Researchers at Stanford University developed a special wound dressing that they report was able to significantly reduce scar tissue caused by incisions.



Results of animal tests and of an early clinical trial of the dressing were "stunning," says Michael Longaker, MD, MBA, who is co-director of the Institute for Stem Cell Biology and Regenerative Medicine and senior author of the study. "It was a surprisingly effective treatment."

Normally, after sutures are removed, the edges of a healing incision are pulled in different directions by the taut, surrounding skin, causing scar tissue to thicken and spread. The novel dressing, which the authors refer to as a "stress-shielding device," eliminates this tension and hence a considerable amount of scarring.

Research on scar formation leads to new understanding of how physical forces alter cell regrowth

Researchers at the institute and their colleagues in the Stanford School of Medicine report that they have identified the molecular pathway through which physical force contributes to scarring in mice.

The study exposes one of the fundamental mechanisms by which the mechanical environment can directly increase inflammation, which is strongly implicated in scarring.
Mice genetically engineered to lack an enzyme that is activated by mechanical force demonstrated less inflammation and fibrosis — the formation of excess fibrous connective tissue — in their incisions than mice in a control group, the study found. Inflammation and scar formation also were reduced among mice injected with an organic compound, a small molecule called PF-573228, that blocks this enzyme, which helps cells sense changes in the mechanical environment.
While further testing is needed to determine the validity of the findings in humans, the researchers say they hope their work will pave the way for new treatments of fibrotic diseases — disorders caused by scarring, such as pulmonary fibrosis (the buildup of scar tissue in the lungs) — as well as inflammatory diseases, such as rheumatoid arthritis.

Study sheds light on stem cell role in regenerating fingers, toes

Tissue-specific adult stem cells are responsible for the ability of mammals to re-grow the tips of fingers or toes lost to trauma or surgery, say researchers at the Stanford University School of Medicine. The finding discredits a popular theory that holds that previously specialized cells regress, or dedifferentiate, in response to injury to form a pluripotent repair structure called a blastema. Instead, Yuval Rinkevich, PhD, a Siebel Scholar in the institute found that each kind of tissue in newly growing fingertips in mice—skin, nerves, bone, etc.—came from different stem cells that were each already dedicated to growing one particular kind of tissue.
“We’ve shown conclusively that what was thought to be a blastema is instead simply resident stem cells that are already committed to become specific tissue types,” said Irving Weissman, MD, director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine. “The controversy about limb regeneration in mammals should be over.”

Enhancement of mesenchymal stem cell repair function through the use of a biomimetic hydrogel

Geoffrey Gurtner, MD and institute co-director Michael Longaker, MD found that using a hydrogel engineered to mimic a natural biological environment, when seeded with certain kinds of stem cells, induced the stem cells to release factors that contributed to the formation of new blood vessels. They also discovered that wounds dressed with the stem-cell-seeded hyrdogel healed significantly faster than wounds that were simply given the stem cells.

Enhancing bone repair by using purified stem cells from a patient’s own fat

Clinically available sources of bone for repair and reconstruction are limited by the accessibility of autologous grafts, the infectious risks of cadaveric materials, and the durability of synthetic substitutes. An approach using a patient’s own bone-generating stem cells would avoid these problems. Geoffrey Gurtner, MD and Michael

Longaker, MD determined that some fat-derived stem cells that create low levels of a certain protein (CD105), when purified and administered in the injury, showed an increased ability to regenerate bone. The research raises the possibility that one day patients with bone defects or injuries may be treated with low-CD105 stem cells purified from their own fat.

Young blood revives aging muscles

Aging muscles don't heal like young ones, but it turns out that's not the muscle's fault. A study led by Thomas Rando, MD, PhD, shows that it's old blood that keeps the muscles down.

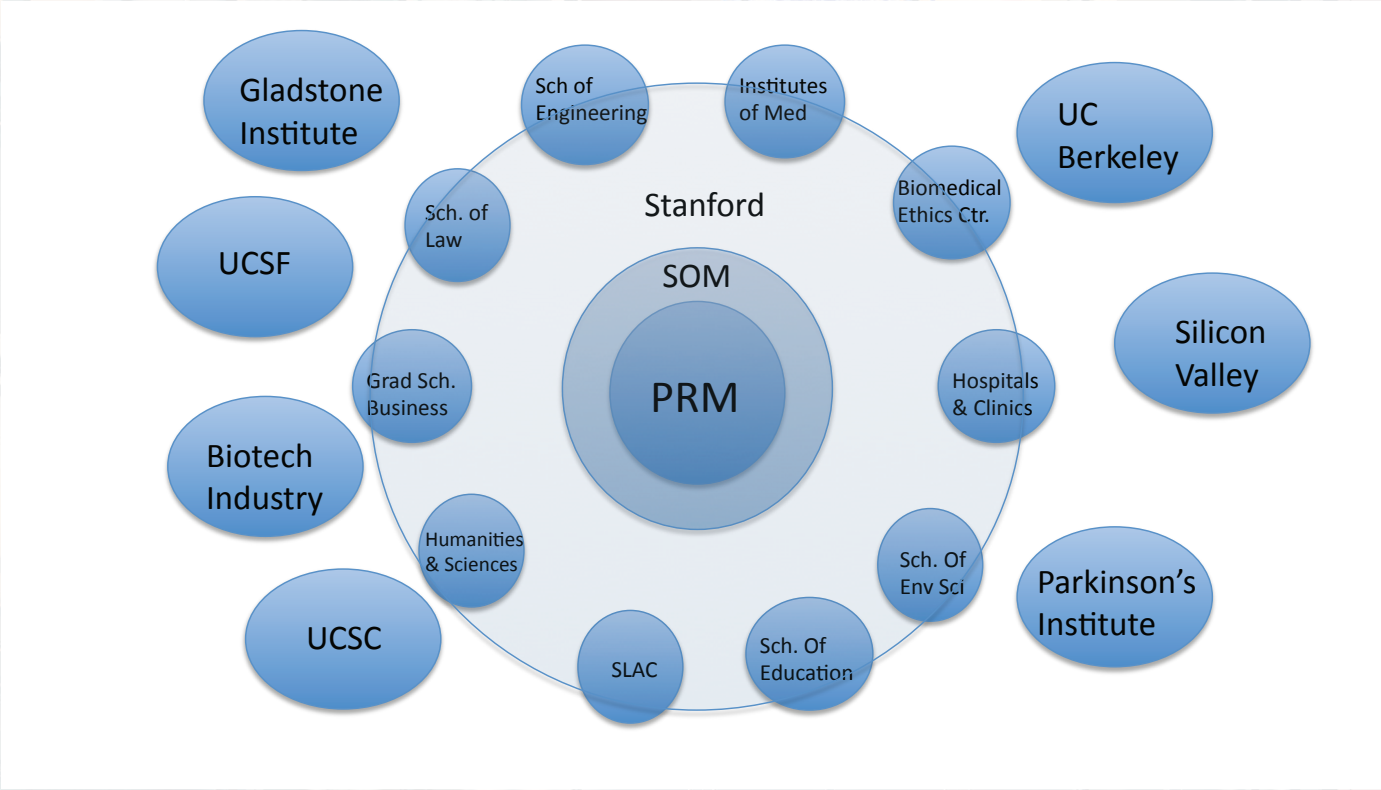
The study built on previous work by Rando, Irv Weissman, MD, Irina Conboy, PhD (now at UC Berkeley) and Amy Wagers, PhD (now at Harvard), which showed that old muscles have the capacity to repair themselves but fail to do so. Rando and his group studied specialized cells called satellite cells, the muscle stem cells that dot muscle tissue. These normally lie dormant but come to the rescue in response to damaged muscle–at least they do in young mice and humans.

In older mice the satellite cells hold the same position but are deaf to the muscle's cry for help. For a study published in the journal *Nature*, Rando and his group first attached old mice to their younger lab-mates in a way that let the two mice share a blood supply. They then induced muscle damage only in the older mice. Bathed in the presence of younger blood, the old muscles healed like a younger mouse's.

"We need to consider the possibility that the niche in which stem cells sit is as important in terms of stem cell aging as the cells themselves," said Rando. It could be the chemical soup surrounding the cells, not the cells themselves, that's at fault in aging.

The Program in Regenerative Medicine

Stem cell science and regenerative medicine research will likely have implications for all arenas of human life, not only in medicine itself, but also in law, economics, business, consumer products, social relationships and ethics. Accordingly, basic and translational research in stem cell science will benefit from the involvement of those from these other spheres.



The Program in Regenerative Medicine (PRM) was established in 2004 to extend research, education and funding initiatives to clinical and science faculty in the School of Medicine, as well as the associated hospitals, and to the other schools at the university. In addition, the PRM reaches beyond the university to involve other university campuses, biotechnology companies and the scientific and business communities in Silicon Valley.

The PRM's primary responsibilities are:

- To plan, develop, build and run stem cell facilities.
- To identify sources of research support in SCBRM and to alert all faculty of these opportunities.
- To develop educational and seminar programs.
- To establish medical ethics and bioethics programs in the ISCBRM.
- To plan programs and identify (and possibly recruit) faculty in the clinical translation of SCBRM discoveries at Stanford and the School of Medicine.

Michael Longaker, MD

New Doctoral Program in Stem Cell Biology and Regenerative Medicine

Interdepartmental Doctoral Program in Stem Cell Biology and Regenerative Medicine

Renee Reijo Pera, PhD

Theo Palmer, PhD

In 2011, the institute began accepting applications for the first class in its new interdisciplinary doctoral program in stem cell biology and regenerative medicine, the first PhD program in the country devoted solely to stem cell biology. The PhD program was approved by the Stanford Academic Senate in April 2011 and is slated to welcome the inaugural class in the fall of 2012.

Of the twelve students offered spots in the program's first class, ten quickly accepted, an acceptance rate that is far higher than is experienced by most doctoral programs.

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. While developmental biology is concerned with the development of tissue, the field of stem cell biology and regenerative medicine also concerns itself with the renewal of tissues by tissue-specific stem cells and the effects of aging, many of which can be traced to the loss of function of pools of tissue-specific stem cells.

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.

CIRM Training Grants

The institute administers a CIRM-funded training grant for full-time research and can fund up to 16 scholars for up to three years. The program includes several unique requirements that make it particularly valuable. For instance, a 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 take several required courses, and non-MD scholars are given a two-week clinical immersion in the area of medicine most closely related to their area of research.

CIRM-funded training in stem cell laboratory techniques

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. Currently, courses are offered free of charge through a grant from the California Institute for Regenerative Medicine (CIRM) and therefore can 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 are:

Basic hESC Biology: This course is one of the central components of the program. It provides the essentials of hESC biology to individuals with little or no previous experience with hESCs. Students learn the basic techniques required to culture, differentiate and analyze hESCs. Students 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.

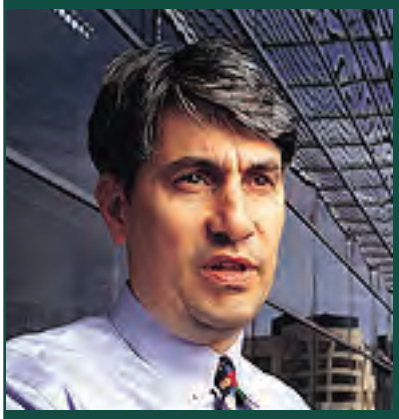
Reprogramming and Somatic Cell Nuclear Transfer (SCNT): This is an advanced technique course that the institute offers at the Center for Human Embryonic Stem Cell Research and Education. Individuals learn basic methods for working with human embryos and SCNT. The center also includes instruction in derivation of induced-pluripotent stem cell lines.

Human Embryonic Stem Cell Derivation: In conjunction with basic stem cell culturing technique, the institute also provides 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 teaches students basic methods (such as in-vitro maturation) for handling and growing early human embryos.

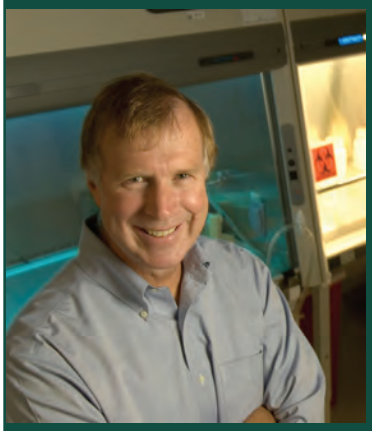
Irving Weissman, MD
Director
Director, Ludwig Center for Cancer Stem Cell Research
Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research

Irving Weissman has directed the institute since its founding, providing the 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 cells 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 in the School of Medicine

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, Center for Human Embryonic Stem Cell Research and Education
Director, Interdepartmental Doctoral Program in Stem Cell Biology and Regenerative Medicine

Renee Reijo Pera focuses on understanding human embryo growth and development, and on characterizing the basic properties of human embryonic stem cells, especially programming and reprogramming in the human embryo and the human germ line. Studies have applications in basic science and in models of human disease including induced pluripotent stem cells and Parkinson's Disease. Her work has fundamentally changed understanding of human preimplantation embryo development. Her laboratory has established techniques for differentiation of human embryonic stem cells to germ cells and somatic lineages, allowing genetic manipulation of these differentiation pathways.

Philip A. Beachy, PhD

Philip 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, PhD

Marius Wernig is interested in two major areas of stem cell biology. One focus is the epigenetic reprogramming of somatic cells into pluripotent stem (iPS) 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 human 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, and with Irv Weissman, the lab is actively developing an anti-CD47 antibody for clinical trials in human AML.

Maximilian Diehn, MD, PhD

Maximilian 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.

Institute Membership

Members:

Beachy, Philip
Developmental Biology

Clarke, Michael
Medicine/Oncology

Diehn, Maximillian
Radiation Oncology

Longaker, Michael
Surgery/Plastic & Reconstruct.

Majeti, Ravindra
Medicine/Hematology

Palmer, Theo
Neurosurgery

Reijo Pera, Renee
Obstetrics and Gynecology

Weissman, Irving
Pathology

Wernig, Marius
Pathology

Associate Members with lab space in the Lorry I. Lokey Stem Cell Research Building

Brunet, Anne

Cheshier, Samuel

Cleary, Michael

Cooke, John P.

Daldrup-Link, Heike

Feldman, Brian

Kim, Seung K.

Kuo, Calvin

Malenka, Robert

Mitchell, Beverly

Monje, Michelle

Nusse, Roeland

Quake, Steve

Sage, Julien

Shizuru, Judith

Sweet-Cordero, Alejandro

Weinberg, Kenneth

Wu, Joseph

Wysocka, Joanna

Yang, Fan

Associate Members:

Altman, Russ
Bioengineering

Andreasson, Kati
Neurology

Artandi, Steve
Medicine/Hematology

Attardi, Laura
Radiation Oncology

Axelrod, Jeff
Pathology

Baer, Thomas M.
Applied Physics

Baker, Bruce
Biology/Emeritus

Baker, Julie
Genetics

Barres, Ben
Neurobiology

Barron, Annelise
Bioengineering

Behr, Barry
Obstetrics and Gynecology

Berg, Paul
Biochemistry

Bergmann, Dominique
Biology

Blau, Helen
Microbiology & Immunology

Bogyo, Matt
Pathology

Brunet, Anne
Genetics

Butte, Atul
Medicine/Pediatrics

Calos, Michele
Genetics

Chang, Ching-Pin
Med/Cardiovasc. Medicine

Chang, Howard
Dermatology

Chen, Chang-Zhen
Microbiology & Immunology

Chen, James
Chemical & Systems Biology

Cheng, Alan
Otolaryngology/Head & Neck Surgery

Cheng, Ivan
Orthopaedic Surgery

Cheshier, Samuel
Neurology and Neurological Sciences

Clandinin, Thomas
Neurobiology

Cleary, Michael
Pathology

Cochran, Jennifer
Bioengineering

Cooke, John P.
Med/Cardiovasc. Medicine

Daldrup-Link, Heike
Radiology

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

Institute Membership

Giaccia, Amato
Radiation Biology

Gonzalgo, Mark
Urology

Gozani, Or
Biology

Graef, Isabella
Pathology

Gurtner, Geoff
Surgery/Plastic & Recons.

Hanawalt, Philip
Biology

Heilshorn, Sarah
Materials Science & Eng.

Heller, H Craig
Biology

Heller, Stefan
Otolaryngology

Helms, Jill
Surgery/Plastic & Reconstructive

Hsu, Teddy
Obstetrics and Gynecology

Kennedy, Donald
Honorary

Khavari, Paul
Dermatology

Kim, Seung K.
Developmental Biology

Kovacs, Gregory
Electrical Engineering

Krasnow, Mark
Biochemistry

Kuo, Calvin
Med/Hematology

Levenston, Marc
Mechanical/Biomechanical Engineering

Liao, Yaping
Ophthalmology

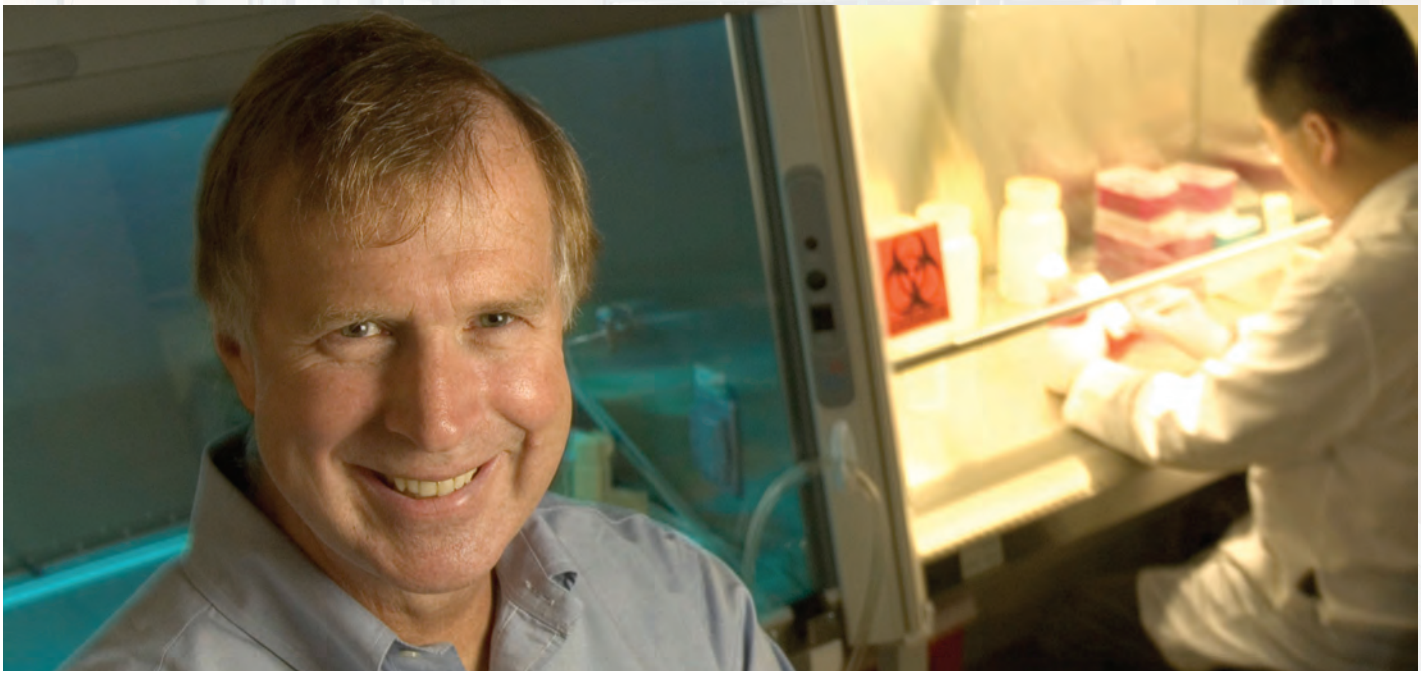
Lipsick, Joseph
Pathology

Lowe, Anson
Medicine - Gastroenterology

Lowe, Christopher
Biology

Lu, Bingwei
Pathology

Luo, Liqun
Biology



Malenka, Robert
Psychiatry & Behavioral Sciences

McConnell, Susan
Biology

Mitchell, Beverly
Med/Oncology

Monje, Michelle
Neurology and Neurological Sciences

Nusse, Roeland
Developmental Biology

Oro, Anthony
Dermatology

Pasricha, Pankaj Jay
Gastroenterology & Hepatology

Peehl, Donna
Urology

Penn, Anna
Pediatrics – Neonatology

Quake, Steve
Bioengineering

Rando, Tom
Neurology

Recht, Lawrence
Neurology

Reiss, Allan
Interdisciplinary Brain Science Research

Rosen, Glenn
Med/Pulmonary & Critical Care Medicine

Rutt, Brian
Radiology - Diagnostic

Sage, Julien
Pediatrics/Cancer Biology

Sakamoto, Kathleen
Pediatrics–Oncology/ Hematology

Schnitzer, Mark
Biology & Applied Physics

Scott, Matthew
Developmental Biology

Shizuru, Judith
Med/ Blood & Bone Marrow Transplantation

Shortliffe, Linda
Urology

Simon, Michael
Biology

So, Samuel
General Surgery

Stearns, Tim
Biology

Steinberg, Gary
Neurosurgery

Sunwoo, John
Otolarynogology

Sweet-Cordero, Alejandro
Pediatrics/Cancer Biology

Talbot, William
Developmental Biology

Wandless, Thomas
Chemical & Systems Biology

Weinberg, Kenneth
Pediatric Stem Cell Transplantation

Wong, Albert
Neurosurgery

Wu, Joseph
Medicine & Radiology

Wysocka, Joanna
Chemical & Systems Biology

Yang, Fan
Orthopedic Surgery and Bioengineering

Yang, Phillip
Med/Cardiovascular Medicine

Yock, Paul
Med/Cardiovascular Medicine

Grants –New in 2011

Beachy, Philip
Epithelial/Stromal Signaling in Bladder and Prostate Cell Proliferation
National Institutes of Health
$1,752,569

Beachy, Philip
Hedgehog Signaling in Breast Cancer: Tumor-Stroma Interactions and the Growth of Tumor Initiating Cells
Susan G. Komen Breast Cancer Foundation
$ 180,000

Boiko, Alexander D.
Isolation and Characterization of Tumor Stem Cells from Melanoma Patients
National Institutes of Health
$307,907

Clarke, Michael F
Cellular and Molecular Characterization of ER + Breast Cancer
Department of the Army
$7,978,115

Clarke, Michael F
USP16 Controls Stem Cell Number: Implications for Down Syndrome
California Institute for Regenerative Medicine
$1,264,032

Lu, Wan-Jin
The Role of Injury-Inducible Epithelial/Stromal Feedback Signaling Pathways in Bladder Cancer
Damon Runyon Cancer Research Foundation
$156,000

Reijo Pera, Renee
Stanford University Center for Reproductive and Stem Cell Biology
National Institutes of Health
$8,520,887

Reijo Pera, Renee
Correlated time-lapse imaging and single cell molecular analysis of human embryo-development
California Institute for Regenerative Medicine
$1,260,122

Sahoo, Debashis
Application of Boolean networks to discover stem and progenitor cells
National Institutes of Health
$152,135

Weissman, Irving
Antibody tools to deplete or isolate teratogenic, cardiac, and blood stem cells from hESCs
California Institute for Regenerative Medicine
$1,471,253

Weissman, Irving
Molecular Characterization of Acute Myeloid Leukemia
National Institutes of Health
$1,850,742

Irv Weissman, MD

Wernig, Marius
Testing synaptic properties of human neurons derived from Fragile-X patients
Department of the Army
$483,991

Wernig, Marius
Cellular tools to study brain diseases affecting synaptic transmission
California Institute for Regenerative Medicine
$1,906,494

Marius Wernig, MD

Wernig, Marius
Developing induced neuronal cells to model human brain disease
The New York Stem Cell Foundation
$1,500,000

Total:
$28,784,247

Stem Cell Development Efforts 2011

As the saying goes, "it takes a village"… At Stanford's Institute for Stem Cell Biology and Regenerative Medicine, it takes a village of donors and organizations to advance our research in the hope of delivering new and effective therapies to patients with a multitude of diseases and disorders. Thanks to the generosity of individual donors and funding from the California Institute for Regenerative Medicine (CIRM), we raised millions of dollars in 2011. This funding was critically important for our programmatic needs since we were able to shift our focus from capital fundraising for the Lorry I. Lokey Stem Cell Research Building to what is happening within our labs.

More specifically, our foremost fundraising priority is providing a consistent source of funding to support the work being done by the faculty who come from a broad range of departments and give the institute its breadth. Looking outward, the Lokey building's space for more than 500 individuals will allow for growth over time in order to accommodate rotating guest benches and further recruitments of leading stem cell scientists and their research teams. However, given that the National Institutes of Health (NIH) funding does not cover recruitments, we still need to raise funds for this purpose.

We are on the cusp of a pivotal new era at the institute, one in which we will conduct definitive clinical trials

Additionally, in order to recruit and retain extraordinary faculty, we need to equip them with the tools necessary for their research. The institute's many scientists are on the brink of exciting stem cell discoveries using innovative techniques with the aid of existing equipment. However, in order to provide for the large number of diverse teams that work in the building, current equipment needs to be augmented and funding is required for additional new and specialized technological tools that lie at the cutting edge of stem cell research.

To date, philanthropy has allowed us to advance research to the point of shifting our focus toward translational medicine. In fact, we are on the cusp of a new pivotal era at the institute; one in which we will conduct definitive clinical trials. However, in order to maintain this momentum, the institute must rely on private funds to establish the first-ever Stem Cell Translational Center and thus explore how to hasten discoveries into therapies.

Funding from CIRM, private sources and the NIH each play a significant role in the institute's budget. However, due to diminished funding from federal agencies and the slow economic recovery, we have had to recalibrate our financial goals, while still maintaining a sense of urgency to our research. Thus, in this restricted and constantly changing grant environment, the institute must depend on other sources for ongoing support to continue our important work. The sustained generosity of individual and institutional donors is critical to all that we do, and having that support will directly impact our ability to improve the lives of patients and their families.

We have come so far, and yet so much remains to be done. We are committed to leading the world not only in stem cell research, but also in the next phase of translational medicine. With this in mind, we thank you for your ongoing interest in the next chapter of Stanford's groundbreaking work in stem cell biology and regenerative medicine.

Philip Beachy

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Irving Weissman

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