



Stem Cell Building Dedication



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Purified blood stem cell transplant surprise

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Lorry I. Lokey Stem Cell Research Building Officially Opens

Researchers, donors, and university and state officials gathered October 27th for the dedication of the Lorry I. Lokey Stem Cell Research Building. The building, which is the largest stem cell research facility in the country, will bring together stem cell researchers from across the campus, fostering an interactive and scientifically creative environment. But first researchers have to unpack.

“We’ve got boxes all over the place,” said associate professor of neurosurgery Theo Palmer, PhD, one of the first to move in. “But we’re really excited. We’re in a beautiful building with extraordinary resources. And our collaborators are close by. Now, instead of making a plan to go meet and talk with someone 20 minutes away, we’ll be bumping in to them in the hallway.”

At a symposium before the dedication, Irving Weissman, MD, director of the Institute for Stem Cell Biology and Regenerative Medicine, spoke about the process of getting to this day and the promise of stem cell research in the future. Speaking at the dedication itself were Dean

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Lokey dedication

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of the School of Medicine Philip Pizzo, MD, Stanford University President John Hennessy, and Leslie Hume, Chair of the Stanford University Board of Trustees. Also speaking were benefactor Lorry Lokey and Robert Klein, the chair of the governing board of the California Institute for Regenerative Medicine (CIRM).

“The Lokey Building is the first of our Stanford Institutes of Medicine and is emblematic of Stanford’s past and symbolic of our future,” said Dean Pizzo. , “This incredible new laboratory facility is built on a design championed by faculty to facilitate research in one of the most exciting interdisciplinary areas of the 21st century — stem cell biology and regenerative medicine. It is a beacon of hope at the intersection of science and medicine, promoting discovery and innovation for the care of children and adults facing serious illness.”

“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.” Details like the highest ratio of laboratory support space — the housing for large centrifuges, freezers, tissue culture rooms and more — to working space (about 1:1, versus about 0.3 to 1 in older research buildings in the medical school). Details like a dedicated tissue bank to store stem cell lines and animal and human tissues, a microfluidics core to collect and analyze the extremely rare cells and an in vivo imaging core to visualize stem cells in the body. Details like a state-of-the-art animal research facility with biometric entry codes, air showers and recyclable mouse cages.

The entire facility represents an unprecedented commitment to the promise of all types of stem cell research — from stem cells derived from embryos to induced pluripotent stem cells (or iPS cells) derived from fetal or adult tissues to cancer stem cells that give rise to tumors and cause disease relapses. Stem cell researchers have long maintained that it is critical

to continue to conduct research on all types of stem cells, which have the capacity to become many types of cells and tissues, in order to move the field forward more quickly. Bringing all of these researchers under one roof will enable easy collaboration and data sharing, and together they can benefit from the advanced equipment and technical support available in the core facilities.

The ability of stem cells to renew themselves and to become various tissues holds great medical promise. The first clinical trial of human embryonic stem cells was recently launched to test the cells’ ability to regenerate spinal cord neurons in recently paralyzed patients.

“Stem cells are going to be as significant as the silicon chip that created Silicon Valley,” said philanthropist Lokey, the major benefactor for the building, with a gift of \$75 million. “Stem cells are going to introduce an entirely new field of medicine for extending lives and improving the quality of life.”

CIRM’s Robert Klein 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,” said Klein. “While federal stem cell research funding suffers tragic, periodic setbacks and restrictions, Stanford’s stem cell institute will serve as a beacon of strength and global leadership, and provide a safe harbor for the cutting edge of science.”



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

Researchers at the Stanford University School of Medicine 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.

The study, led by Judith Shizuru, MD, PhD, associate professor of medicine, was published online Aug. 2 in the Proceedings of the National Academy of Sciences. Bone marrow transplantation has long been a powerful therapy in combating cancer and other disorders, but it also involves serious risks that make physicians wary. Patients getting bone marrow transplants must first be given powerful drugs or radiation treatments that wipe out their own bone marrow and immune cells, leaving them vulnerable to life-threatening infections.

The patient's supply of blood and immune stem cells is then replenished by bone marrow from a donor, but this bone marrow also contains mature immune cells called T cells that can see the patient's tissues as immunologically foreign. T cells that react against patient tissues cause a disorder called graft versus host disease, or GVHD, which can severely damage the patient's body.

Conventional wisdom among transplantation specialists has been that the bone marrow transplant should contain some T cells from the donor. Although the presence of mature donor T cells is known to cause GVHD, it is generally believed that these T cells can help protect the patient from infectious disease and fight cancer until the transplanted stem cells can mature into a new immune system. It is also thought that the presence of mature T cells decreases the chance that the patient will reject the graft.

"People think that T cells are a necessary evil because they help with engraftment and immune reconstitution," Shizuru said. For these reasons, patients are not given pure blood-forming stem cells as part of current therapy.

The new research by Shizuru, lead author and research associate Antonia Mueller, MD, and their colleagues calls into question those assumptions. When they 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. T cells from the donor seemed to work against the grafted stem cells and inhibit their maturation into mature immune cells. Furthermore, Shizuru said follow-up studies showed that the donor's T cells did not help eradicate pathogens.

The current research enlarges on work done by Shizuru last year, in which she and her colleagues compared the effectiveness of purified stem cells with unmanipulated bone marrow cells containing low levels of T cells.

In the new study, Shizuru and her colleagues took a more precise look at the action of the mature T cells by comparing how well both groups of mice were able to regenerate bone marrow, blood and lymphoid tissues in the early post-transplant period (within one week) up through one year after transplantation. Although the work was done in mice, Shizuru believes the results will be medically pertinent. "In our studies we tried to replicate the human system, and I believe what we have found is applicable to humans," she said.



For more information, go to stemcell.stanford.edu

Melanoma-initiating cells identified by study

Scientists at the School of Medicine have identified a cancer-initiating cell in human melanomas. The finding is significant because the existence of such a cell in the aggressive skin cancer has been a source of debate. It may also explain why current immunotherapies are largely unsuccessful in preventing disease recurrence in human patients.

“These cells lack the traditional melanoma cell surface markers targeted by these treatments,” said postdoctoral scholar Alexander Boiko, PhD. “Without wiping out the cells at the root of the cancer, the treatment will fail.”

Boiko is the first author of the research, published in the July 1 issue of *Nature*. He works in the laboratory of Irving Weissman, MD, the director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine. Weissman is the medical school’s Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research and the senior author of the research. He is also a member of the Stanford Cancer Center.

The cancer stem cell theory holds that, like queen bees in a hive, only a subset of cancer cells are at the root of the tumor’s growth. These cells can both self-renew (that is, make more of themselves) and differentiate into other tumor cell types.

Any therapy that doesn’t wipe out these elite cancer stem, or initiating, cells has no chance of completely eradicating the disease even if it destroys nearly all other tumor cells. That’s why, say proponents, it can be relatively easy to get a patient into remission, but extremely difficult to prevent the cancer stem cells from roaring back and causing a relapse months or years later.

Cancer stem cells were first identified in blood cancers, but have since been identified in a number of solid tumors including bladder, brain, breast and colon cancers. Previous studies in the laboratory of assistant professor of radiation oncology Maximilian Diehn, MD, PhD, in collaboration with the laboratories of Weissman and Stanford colleague Michael Clarke, MD, have indicated that cancer stem cells may be

more resistant than other cancer cells to many common treatments like radiation and some chemotherapies. Clarke is the Karel H. and Avice N. Beekhuis Professor in Cancer Biology at the medical school and both Diehn and Clarke are members of the Stanford Cancer Center.

Although a growing body of evidence seems to support the cancer stem cell hypothesis, melanoma has remained a conundrum. A University of Michigan study in 2008 found that as many as one in four melanoma cells could cause cancers in immune compromised mice, suggesting that there may not be a particularly privileged subset of cancer stem cells in this tumor type. Boiko set out to solve the mystery.

“I didn’t know if melanoma would in fact have the cancer-initiating cells,” said Boiko. “I was completely unbiased, so I was actually sort of surprised to find such a clear-cut answer. It fits exactly what’s been discovered in the studies of other solid tumors.”

To conduct the study, Boiko analyzed cell surface markers on primary melanoma tumor samples taken directly from patients at the Stanford Cancer Center. He found that one protein, called CD271, was always expressed on only a fraction of the cells in the human melanoma samples tested. Further studies strongly suggested that CD271 cells are melanoma precursors. In addition to Boiko, Weissman, and Longaker, other Stanford researchers involved in the work include assistant professor of surgery George Yang, MD, postdoctoral scholars Olga Razorenova, PhD, and Daphne Ly, MD; professor of pathology Matt van de Rijn, MD; professor of dermatology Susan Swetter, PhD; associate professor of surgery Denise Johnson, MD; Paris Butler, MD; otolaryngologist Benzion Joshua, MD; and professor of otolaryngology and neurosurgery Michael Kaplan, MD.

The research was supported by the National Institutes of Health, the American Cancer Society, the Virginia & D.K. Ludwig Fund for Cancer Research, the Oak Foundation and the Ellenburg Faculty Scholar Endowment.

Antifungal slows tumor growth in mice

A common antifungal medication can slow tumor growth in mice, according to scientists at the Stanford University School of Medicine. The drug, called itraconazole, inhibits a molecular pathway 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, said the researchers.

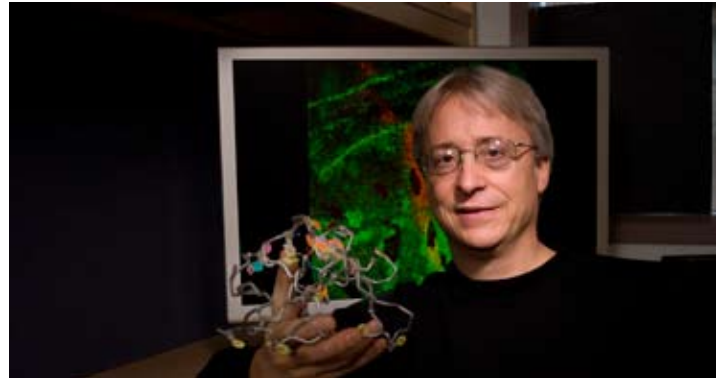
“There is a fairly broad range of tumors in which this molecular cascade, called the ‘Hedgehog’ pathway, plays an important role,” said developmental stem cell biologist Philip Beachy, PhD. “The virtue of screening existing drugs is that you already have all the information about dosage and toxicity, and you can move into clinical trials fairly readily.”

Although itraconazole alone doesn’t eliminate the tumor, the researchers hope that combining the treatment with other therapies that target the same critical pathway may be a valuable option for many patients.

Beachy and his colleagues have spent many years understanding the Hedgehog pathway - a series of molecular events that help cells to know where they are in the body by sensing external signals called Hedgehog proteins. These Hedgehog proteins constitute a family of signals that are important not only during fetal development, but also in many cancers.

The pathway’s importance has made it an attractive target for drug development companies, many of which are trying to engineer new molecules to block it. Beachy and his colleagues took a slightly different approach by choosing to screen drugs already available to see if any were able to trip up the molecular relay.

The researchers applied about 2,400 drugs to cells specially engineered by Beachy to emit a light signal when the Hedgehog pathway is active. The drugs were either already approved by the U.S. Food and Drug Administration or had undergone human safety testing



during early stages of the approval process. They then stimulated the pathway in the cells in laboratory dishes and looked to see which drugs blocked the signal. 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 one drug, itraconazole, an orally administered antifungal medication that can be safely taken for several months, showed promise. The dose needed to block the Hedgehog pathway in the cells is similar to that used to combat the severe fungal infections that can develop in people whose immune systems are weakened by AIDS or cancer.

In mice, the researchers found that oral itraconazole treatment significantly slowed the growth of tumors implanted under the skin for up to 18 days. In contrast, the control mice’s tumors had grown so large during this time that the animals had to be euthanized. Adding cyclopamine had an even stronger effect, showing that the two drugs work on the pathway in different, yet complementary, ways.

Beachy and his colleagues are now discussing the use of itraconazole in human clinical trials in patients with skin and urologic cancers. They are also seeking other molecules that can be combined with itraconazole to block the Hedgehog pathway.

The research was supported by the Prostate Cancer Foundation, the Stanford University Center for Children’s Brain Tumors, the National Institutes of Health and the Howard Hughes Medical Institute.

Center for Human
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NEWS

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 at the [Stanford University School of Medicine](#) have shown that they can predict with 93 percent certainty which fertilized 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. Because the parameters measured in this study occur before any embryonic genes are expressed, the results indicate that embryos are likely predestined to survive or die before even the first cell division. Assessing these parameters in the clinic could make it easier for in vitro fertilization specialists to select embryos for transfer for a successful pregnancy.

“Until recently, we’ve had so little knowledge about the basic science of our development,” said the study’s senior author [Renee Reijo Pera](#), PhD. “In addition to beginning to understand more about our development, we’re hopeful that our research will help improve pregnancy rates arising from in vitro fertilization, while also reducing the frequency of miscarriage and the need for the selective reduction of multiple embryos.”

Reijo Pera is a professor of [obstetrics and gynecology](#) at the medical school and the director of the [Center for Human Embryonic Stem Cell Research and Education](#) at Stanford’s [Institute for Stem Cell Biology and Regenerative Medicine](#). The study was published online Oct. 3 in *Nature Biotechnology*. Postdoctoral

scholar [Connie Wong](#), PhD, and former postdoctoral scholar [Kevin Loewke](#), PhD, are the co-first authors of the research.

Currently, clinicians monitor embryonic development for three to five days in an attempt to identify those that are more likely to result in healthy pregnancies after transfer. Despite their best efforts, though, they have only about a 35 percent success rate.

Reijo Pera and her colleagues received a large grant from an anonymous donor to investigate ways to better predict embryonic developmental success within one or two days of fertilization. Not only would such an advance decrease the likelihood of miscarriage or the possible need for a selective reduction, it would also reduce the amount of time the embryo would have to be cultured in the laboratory before transfer.

The researchers also highlight why it is important to work with human embryos to understand human development. “In mice, about 80 to 90 percent of embryos develop to the blastocyst stage. In humans, it’s about 30 percent,” said Reijo Pera. “In addition, about one in 100 mouse embryos are chromosomally abnormal, versus about seven out of 10 human embryos. That’s why human studies like these are so important. Women, their families and their physicians want to increase the chances of having one healthy baby and avoid high-risk pregnancies, miscarriages or other adverse maternal and fetal outcomes. It’s truly a women’s health issue that affects the broader family.”

A longer version of this article can be found at: <http://stemcell.stanford.edu/news>

Weissman takes the lead in fighting stem cell fraud

Buyer beware: Stem cell charlatans are marketing unproven and potentially lethal treatments to desperate patients and their families through the Internet.

Irving Weissman, MD, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, warns that more than 200 websites are preying on patient hopes for miracle stem cell cures of most every medical condition.

The International Society for Stem Cell Research, of which Weissman is immediate past president, recently launched a website to help patients and their families learn more about stem cell biology. The website suggests questions to ask when vetting clinics and provides an avenue to begin investigations of what may be fraudulent claims about stem cell treatments.

Weissman, who is senior author of the report, “Patients Beware: Commercialized Stem Cell Treatments on the Web,” published this month in *Cell Stem Cell*, also notes that unscrupulous stem cell merchants frequently attach the names of reputable medical experts without their knowledge, invent patient testimonials and, in essence, do whatever it takes to profit off the seriously ill. Unproven, but there is currently no clearing house for reliable information about what stem cell treatments are worthwhile and which are not. The use of quotes from well-regarded stem cell scientists and physicians is not uncommon on unscrupulous Internet websites, according to

Weissman. Frequently these experts are unaware that their names are being used, and the quotes are fabricated or taken out of context from some other source.

As a result of the task force’s efforts to publicize these and other abuses, the ISSCR recently launched a publicly available website (www.closerlookatstemcells.org) where patients can learn more about stem cell biology, learn what questions to ask of potential clinics and even submit a specific website for further investigation by the ISSCR. When a company or clinic is submitted for investigation, the ISSCR will evaluate whether a medical ethics committee is involved to protect the rights of a patient and whether the proposed treatment will be supervised by an official regulatory body such as the European Medicines Agency or the U.S. Food and Drug Administration. It will provide the results of the inquiry on the patient website.

“If you think about this, it’s an amazingly unusual thing for a body of scientists to do,” said Weissman of the website. “Once you read those websites and see what they are doing to people, you begin to lose faith in human nature. They will take the last dollars and days of people’s lives. But by asking a few simple questions, you’ll learn whether they are trying to treat you — or your wallet.”

hESC Classes in iPS Cell Techniques

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

Apply at:

<http://hesc.stanford.edu/education/apply.html>



CIRM NEWS

News and Information from the
California Institute for Regenerative Medicine

CIRM awards researcher \$2.3 million to develop stem cell therapy for muscular dystrophy

[Michele Calos](#), PhD, professor of genetics at the [Stanford University School of Medicine](#), has received \$2.3 million from the [California Institute for Regenerative Medicine](#) to develop a stem cell-based therapy for Duchenne muscular dystrophy. The award was part of \$67 million distributed today by the institute to enable the rapid movement of promising basic stem cell science out of the laboratory and into clinical applications.

The grants represent the second round of the institute's Early Translational Awards, which are expected to either result in or make significant strides toward a candidate drug or cell therapy for human disease. The ultimate goal of the awards is to develop therapies for submission to the [Food and Drug Administration](#) for approval for use in clinical trials. The institute expects to award such grants on a 12- to 18-month cycle.

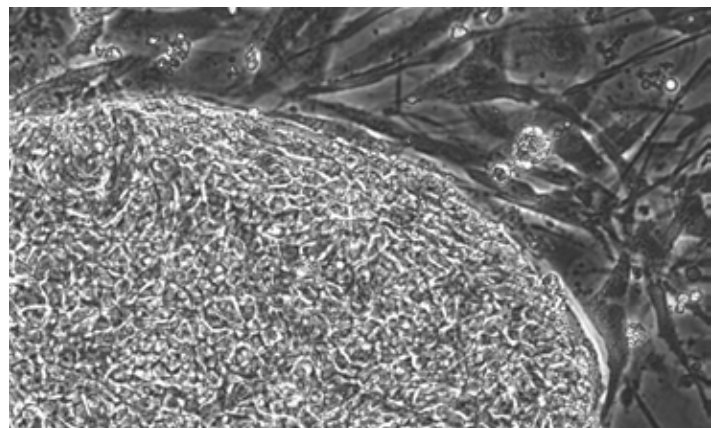
"This second round of Early Translational Awards will strengthen CIRM's portfolio of future therapies," said CIRM president Alan Trounson, PhD, in a statement distributed by the institute. "We are looking for ways to complement our leading edge of stem cell-based treatments for patients and these projects will load our frontline portfolio with promising studies on autism, muscular dystrophy, Canavan disease and liver disease. These projects will enhance the potential medical options available for patients and hopefully in the near future produce cures for such debilitating

handicaps and diseases."

Calos received the award to investigate how to reprogram adult cells from skin or fat to become muscle-generating stem cells expressing the protein missing in people with Duchenne muscular dystrophy, the most common childhood form of the disease.

Calos and her lab members have developed a mouse model of the disease in which to conduct their experiments; they will then pursue a similar strategy in cells from patients with DMD. If successful, the researchers will develop standard procedures to test and ensure the safety of the cells for eventual use in humans with DMD and possibly other degenerative disorders.

With these grants, Stanford has now received a total of about \$175 million from CIRM.



Upcoming CIRM Events:
ICOC meeting,
November 11, 2010

Scientific and Medical Accountability Standards
Working Group
Nov. 22, 2010