Message from the Director 1

Research 5
  Cancer 6
  Tissue-Specific (Adult) Stem Cells 20
  iPS and Embryonic Stem Cells 14

Institute Leadership 24

Education 26

2014-2015 Publications 27
Message from the Director

When the Institute for Stem Cell Biology and Regenerative medicine was founded at Stanford over a dozen years ago, the intention was that it would not only be a center of research and discovery, but that it would also be dedicated to translating laboratory science into therapies that would actually improve the lives of sick people. Over the last few years, and this year especially, we are seeing that intention play out in concrete ways.
Thirty years ago, no scientist would think that a discovery they had made had any relevance in the short term to people’s health, or gave much thought to translating their discoveries into actual therapies. Things have changed, not only because the techniques of molecular biology and stem cell science have advanced so rapidly, but also because young students are increasingly interested in how their discoveries might benefit people in their lifetime.

This is nowhere more true than here at the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Let me give you a few examples. Over the last many years, researchers here at the institute have made some very basic discoveries. Those researchers are now actively developing those discoveries with an intent that it may lead to cures for cancers and a number of genetic and autoimmune diseases.

The finding from my laboratory along with the Ravi Majeti lab many years ago that blood cells carry a “don’t eat me” signal called CD47 has now become the basis for a phase I clinical trial of a therapy against all kinds of cancers. The trial of this therapy, which allows immune cells called macrophages to identify and consume cancer cells, is being carried out only at Stanford and the University of Oxford in England.

There are many great examples of basic findings that have real potential to address a huge impediment to curing many diseases: the tremendous toxicity of radiation or chemotherapy treatments that are needed to clear out native blood stem cells, clearing the way to bring in stem cells that will not cause disease.

Recently, Hiro Nakauchi, MD, PhD, was pondering a basic science question about which kinds of amino acids were best to include in a cocktail to feed mouse blood-forming stem cells in a dish. He made the startling discovery that omitting one particular amino acid made the stem cells die. He then made the leap to feeding mice on an artificial diet deficient in only that particular amino acid. In a week, their blood formation went to almost zero. This is a result that usually requires the administration of a heavy dose of chemotherapy or radiation, such as during preparation for bone marrow transplantation.

He then asked, “If I have killed off all the blood stem cells, will this open up places for new stem cells to engraft?” This led him and his team to research the amino acid requirements for human blood-forming stem cells and to explore those requirements in mice with human blood-forming stem cells already engrafted. This research may become the basis for a completely new and far less toxic way to prepare patients for blood stem cell transplantation.

Another example: Angieszka Czechowicz and Deepta Bhattacharya in my lab showed several years earlier that blood stem cells could be depleted artificially in immune-deficient mice by using an antibody to “kit” receptors on stem cells. The lab went on to find that immune-deficient mice could be prepared for the transplantation of healthy blood-forming stem cells using antibody treatment alone, and this could be accomplished
with one to three shots of the antibody. My lab and that of Judy Shizuru, MD, have extended this finding to human blood-forming stem cells that have been transplanted into mice. Monoclonal antibodies that block the human cKit protein deplete human stem cells in immune deficient mice. This is the beginning of a clinical trial to replace chemotherapy with antibodies for the treatment of children with severe combined immune deficiency (SCID), a trial led by Shizuru and Maria Grazia Roncarolo, MD.

But the anti-cKit antibody does not work on normal, non-immune deficient mice. My lab and the Shizuru lab have now overcome that barrier and have shown that the anti-CD47 molecule can synergize with the anti-cKit antibody to prepare immune-competent animals for stem cell transplantation without preparation via chemotherapy or radiation.

This work opens the door to consider antibody conditioning for all blood stem cell transplants, not just in immune competent mice, but in humans with a fully competent immune system. Combining that with the Nakauchi lab diet conditioning should make it possible to make stem cell transplantation an outpatient procedure, and treat a plethora of diseases that we know normal stem cells can overcome. These include sickle-cell disease, Mediterranean anemia, early stage juvenile diabetes, multiple sclerosis, systemic lupus, and many more.

Another great example of a basic science discovery with the potential to provide a number of clinical dividends initially came from my lab and that of Mike Clarke, MD, when we found certain genes that are required for blood-forming stem cells to self-renew. Later, the Clarke lab and other labs showed these genes were required for the normal operation of brain stem cells and peripheral nervous system stem cells. This work lead Clarke to discover a particular gene on human chromosome 21 that was in the pathway. Clarke, a trained hematologist/oncologist, knew that children born with three copies of chromosome 21 universally develop Down syndrome. Three doses of the gene rather than two causes many of the abnormalities common to Down syndrome, but also prevents the development of breast cancer and some other types of cancer. Mike has tracked down the gene and is exploring whether he might develop molecules that could be used to regulate the dose of these genes and become a therapeutic agent for newborns discovered to have Down syndrome.

Other institute scientists are on the path to making similar laboratory to clinic translations. Marius Wernig, MD is leading the way in showing how skin cells can be directly transformed into neural stem cells. Michelle Monje, MD, PhD has shown how normal brain activity fuels the growth of brain cancer, opening up a possibility that inhibiting the molecules that provide this growth signal could inhibit the growth of the brain cancer itself.

That is why I said at the very beginning that discoveries at the very basic level can, in our times, lead to preclinical studies and eventually full translational discoveries to patients. But we have to acknowledge that this progress is dependent on monetary support for leading-edge stem cell research. This is a message that needs to go forth to the US National Institutes of Health and to the people who govern funding levels at the NIH. In California we are blessed that the
people voted for proposition 71, which funded the California Institute for Regenerative Medicine (CIRM). CIRM provides support not only for basic discoveries in all areas of stem cell research, but also provides special funds to carry out a limited number of the discoveries through pre-clinical testing and, if warranted, all the way through early phase clinical trials. Funded adequately, these initiatives support preclinical research and early preclinical trials allow CIRM to build bridges across the “Valley of Death” that prevents almost all discoveries from reaching clinical translation. CIRM is now nearly eight years into its funding, and although cost savings at CIRM can extend some funding beyond 2016, all of us must evaluate whether the only agency in the world that funds efforts from discovery through early-phase clinical trials should end this decade or if it should be funded long enough to understand the full return on investment that Californians voted for. We at the Stem Cell Institute know that CIRM funding has been essential. CIRM funding was responsible for the partial funding of the Lokey Stem Cell Research Building, the funding of select research projects, as well as funding, in part, the only graduate program awarding a PhD in stem cell biology and regenerative medicine. This funding has been critical for moving discovery to translation, and for supplying new MDs and PhDs with the education necessary to translate stem cell discoveries into regenerative medicine.
From their scientific home in the Lorry I. Lokey Stem Cell Research Building, the largest stem cell research facility in the world, scientists of the ISCBRM are engaged in a wide range of research projects involving cancer stem cells, embryonic and induced pluripotent stem cells, and tissue-specific stem cells.

These projects are oriented both toward understanding stem cells and using this knowledge to improve human health.
Cancer

The application of stem cell biology to cancer research is having a profound impact on our understanding of how cancer arises and propagates.

This year, stem cell science took a major step forward into clinical cancer treatment. The institute has been preparing, or taking part in, clinical trials of therapies that grew out of basic stem cell research. These clinical trials have a potentially huge impact on cancer medicine.
Brain activity stimulates brain tumor growth, study finds

Deadly brain tumors called high-grade gliomas grow with the help of nerve activity in the cerebral cortex, according to a new study by researchers at the Stanford University School of Medicine. The study, conducted in mice with an aggressive human brain cancer implanted in their brains, is the first to demonstrate stimulation of tumor growth by brain activity.

It is rare for an organ's primary function to drive the growth of tumors within it, said Michelle Monje, MD, PhD, senior author of the new study and assistant professor of neurology at the School of Medicine. “We don’t think about bile production promoting liver cancer growth, or breathing promoting the growth of lung cancer,” she said. “But we’ve shown that brain function is driving these brain cancers.”

High-grade gliomas are the leading cause of brain-tumor death in children and adults. Survival rates have scarcely improved in the last 30 years. “Clinically, fighting high-grade gliomas is a lot like trying to fight a forest fire,” said Monje, who is also a pediatric neuro-oncologist at Lucile Packard Children’s Hospital Stanford, where she cares for patients with these tumors. “Our new findings indicate that this metaphorical forest fire has been difficult to extinguish because there is something akin to gasoline seeping up from the soil.”

The tumors studied fell into the broad category of high-grade gliomas: diffuse intrinsic pontine glioma, which strikes school-aged children; pediatric cortical glioblastoma, which affects primarily teens and young adults; anaplastic oligodendroglioma, which affects young adults; and glioblastoma multiforme, which affects older adults. Although these tumors originate in different regions of the brain, all of them originate near or can spread to the cerebral cortex, the brain's highly folded outer layer that helps us perceive the world, form conscious thoughts and use language.

Monje’s team identified a specific protein, called neuroligin-3, which is largely responsible for the increase in tumor growth associated with neuronal activity in the cerebral cortex. Neuroligin-3 had similar effects across the different types of high-grade gliomas, in spite of the fact that the four cancers have different molecular and genetic characteristics.

The Stem Cell Theory of Cancer

The old theory of cancer is that any cell in the body, given the right combination of genetic alterations, can “go rogue” and become cancerous. This theory also holds that most cancer cells can be the cancerous seeds that enable the disease to grow and spread.

The stem cell theory of cancer proposes that cancers arise as a result of the slow accumulation of mutations in stem cells, the only kind of cells that live long enough to acquire all the right mutations. The stem cell theory of cancer also proposes that cancers are like any other organ in the body in that they are maintained and sustained by a small number of cancer stem cells (CSCs). These cancer stem cells exist as a result of multiple mutations that arise over time in the stem cells. They are the only cells that can spread the cancer. Under this model, curing cancer requires clinicians to destroy the cancer stem cells in particular. Once that is accomplished, any other cancer cells will die naturally.
“To see a microenvironmental factor that affects all of these very distinct classes of high-grade gliomas was a big surprise,” Monje said. The identity of the factor was also unexpected. In healthy tissue, neuroligin-3 helps to direct the formation and activity of synapses, playing an important role in the brain’s ability to remodel itself. The new study showed that a secreted form of neuroligin-3 promotes tumor growth.

“This group of tumors hijacks a basic mechanism of neuroplasticity,” Monje said.

To conduct the study, Monje’s team employed optogenetics, a Stanford-developed technique that uses genetic manipulation to insert light-sensitive proteins into specific neurons, allowing the neurons to be activated with the flip of a light switch. Into the cerebral cortex of mice with these light-sensitive proteins, the team implanted cancer cells from a human pediatric cortical glioblastoma. After the tumors became established, neurons near the tumors were activated with light. The team then compared tumor growth between these mice and a control group with implanted tumors but without the nerve activation. Increased tumor proliferation and growth in the mice that received neurostimulation via optogenetics were the first indications that neuronal activity fed the brain tumors.

“We’ve shown that brain function is driving these brain cancers. The team performed follow-up experiments on slices of mouse brain to identify secreted factors that made the tumor cells proliferate. They then conducted biochemical analyses to identify neuroligin-3, confirm that the protein could stimulate tumor growth in cultured samples of several kinds of human high-grade gliomas and study which signals the protein uses within glioma cells to promote their growth.

In addition, the researchers examined neuroligin-3 data from the Cancer Genome Atlas, a large public database of human cancer genetics. More activity of the neuroligin-3 gene in high-grade gliomas was linked to shorter survival time among patients with these tumors. The study’s findings may open doors to new high-grade glioma treatments. Although, in theory, the results indicate that sedating patients to reduce neural activity could reduce brain tumor growth, this is unlikely to be accepted as an ethical or practical cancer therapy. A better approach, Monje said, would be to develop drugs that specifically block the tumor-stimulating activities of neuroligin-3, such as a drug that stops the protein from being secreted into the area around the cancer cells.

The lead authors of the study are graduate student Humsa Venkatesh, MD/PhD student Tessa Johung and postdoctoral scholar Viola Caretti, MD, PhD.

Drug may prevent development of invasive bladder cancer, researchers say

A drug already approved for use in humans may prevent invasive bladder cancer, according to a study by researchers at the Stanford University School of Medicine.

The drug, FK506, is commonly used to suppress the immune system in organ transplant recipients to combat rejection. The researchers found that low doses of FK506, also known as tacrolimus, prevented the development of invasive bladder cancer in 10 out of 10 laboratory mice that were given a carcinogen over five months. In contrast, seven of nine control mice developed
invasive cancers during the same time period. “This could be a boon to the management of bladder cancer patients,” said Philip Beachy, PhD, professor of biochemistry and of developmental biology at Stanford and a Howard Hughes Medical Institute investigator. “Bladder cancer is the most expensive cancer to treat per patient because most patients require continual monitoring. The effective prevention of progression to invasive carcinoma would be a major advance in the treatment of this disease.”

Beachy is the senior author of the study, published Oct. 13 in Cancer Cell. Former postdoctoral scholar Kunyoo Shin, PhD, and former graduate student Agnes Lim, PhD, are the lead authors.

Bladder cancer is the fourth most common cancer in men and the ninth most common in women. Smoking is a significant risk factor. There are two main types of the disease: one that invades the muscle around the bladder and metastasizes to other organs, and another that remains confined to the bladder lining. The noninvasive type, which comprises about 70 percent of all bladder cancers, is treatable. The invasive form is largely incurable and often deadly. It is also expensive and difficult to treat, and the high likelihood of recurrence requires ongoing monitoring after treatment.

Some noninvasive cases will progress to invasive cases. FK506 works, the researchers found, by activating a molecular pathway that signals potential cancer cells to become specialized, nondividing tissue. This keeps them from engaging in the uncontrolled growth that can lead to the invasion of surrounding tissue.

Beachy and study co-authors Joseph Liao, MD, associate professor of urology at Stanford and chief of urology at the Veterans Affairs Palo Alto Health Care System, and Edda Spiekerkoetter, MD, an assistant professor of pulmonary and critical care medicine, now are seeking funding to conduct clinical trials of FK506 on people with localized bladder cancers to learn if the drug can also delay progression of the disease in humans.

Immune cells slap their own “eat me” label on cancer cells

In the past few years, Stanford researchers have been learning how immune cells can spot and destroy cancer cells by looking for an “eat me” label in the form of a protein marker called calreticulin (CRT).

Now, scientists in the laboratory of Irv Weissman, MD have discovered that cancer cells don’t need to exhibit CRT to be destroyed--the immune cells can carry around a supply of CRT and can themselves slap those chemical “eat me” labels on cancer cells before eating them.

“The finding suggests new ways to enhance cancer-fighting therapies and also indicates the causes of, and potentially cures for, currently mysterious blood
There are two important mechanisms that the body uses to weed out cancer and other damaged or diseased cells says Weissman, who is also the Virginia and D. K. Ludwig Professor for Clinical Investigation in Cancer Research. One is programmed cell death (PCD), in which abnormal cells destroy themselves. The other is a mechanism whereby immune cells called macrophages engulf and devour damaged cells. This process, called programmed cell removal, is another critical mechanism that often works alongside programmed cell death. In programmed cell removal, dying or damaged cells are swallowed by macrophages before they release their contents in tissues, which would cause damaging inflammation. Programmed cell removal can also occur independently of programmed cell death to eliminate living cells that are not susceptible to PCD.

Stanford researchers previously found that all kinds of cancer protect themselves from programmed cell removal by displaying a “don’t-eat-me” signal called CD47 to counteract the “eat-me” signal presented by CRT on cancer cells. Clinical researchers in the Stanford Cancer Institute are now conducting a clinical trial of a therapy to see if blocking cancer’s CD47 “don’t-eat-me” signal will allow macrophages to engulf and destroy cancer cells displaying the CRT “eat-me” signal.

But what if cancer cells don’t display the CRT signal? Will those cells still be destroyed by roving immune cells? The current research indicates that they will. Cancer cells can still be attacked because the macrophages themselves carry CRT “eat me” molecules that they can place on the cancer cells. Furthermore, the scientists found the cancer cell’s biochemical pathway that mediates the activity of the “eat me” signal. They found that the signal that promotes destruction of the cancer cell comes about through the activation of what’s called the “toll-like receptor” pathway, a primitive pathway that creates inflammation to protect cells from microbes and other pathogens. This pathway modifies a key enzyme called Bruton’s tyrosine kinase (BTK),

### Marking bladder cancer cells with CD47 could dramatically improve cancer surgery

Institute scientists have shown that using a combination of optical imaging technologies and cancer-specific molecular imaging agents is a potentially powerful strategy to improve cancer detection and enable image-guided surgery. Currently, bladder cancer is primarily managed through endoscopic surgery using white light to spot abnormal cells before cutting them out, but this method misses many cancer cells. Using fluorescently labeled CD47 antibody as molecular imaging agent, the researchers demonstrated consistent identification of bladder cancer cells in surgically removed human bladders. The scientists greatly increased the detection of cancer cells and were able to spot variants of bladder cancer cells that are challenging to find. The researchers concluded that CD47-targeted molecular imaging could improve the diagnosis and surgery of bladder cancer surgery.
which catalyzes the cell-surface exposure of the CRT signal and leads to the removal of the cancer cell by immune cells.

“Understanding the pathways that lead to programmed cell removal is important because we can potentially turn up the activity of the toll-like receptor pathway if we want to improve the cancer-fighting ability of CD47 therapies,” says postdoctoral researcher Mingye Feng, PhD, a Damon Runyon fellow, who is the first author on the paper.

The current research also illuminates a potential cause of a rare childhood blood disorder, Weissman says. “When the BTK gene is disrupted, it leads to a childhood failure to produce antibodies, called Bruton’s X-linked agammaglobulinemia. We have not understood why this happened; we thought it might be caused directly and only by a problem in the activity of the B cells that make antibodies,” he says. “We now think that it might also involve a cell removal problem. The exact targets of the removal by macrophages is yet to be determined.”

New way to sort cells without limitations of traditional methods

A team of Stanford University School of Medicine researchers has come up with a new way of analyzing individual cell types by applying advanced mathematical analysis to the cells’ contents. The method is analogous to analyzing a smoothie to find what fruits went into making it, the researchers say. A paper describing the method, called Cibersort, was published online March 30 in Nature Methods. Analyzing and sorting individual cells according to the proteins they display on their surfaces is an essential part of stem cell science and cancer research. By analyzing these proteins, known as cell surface markers, scientists can figure out what kind of cells they are dealing with and see how the cell samples, taken from an animal over a period of time, change.

With cancer, the presence or absence of certain cell markers can make a huge difference in a patient’s prognosis and what treatments will be most effective. But many kinds of tissue can’t be analyzed easily or accurately using current methods of cell sorting, hampering scientists’ ability to do research and clinicians’ ability to find the most effective therapies for cancer and other diseases.

“The basic problem is that we often want to count cell populations in tissues, but we rely on methods that require tissues to be collected and stored, then separated into individual cells or sliced into sections, and then labeled with antibodies to specific markers,” said Ash Alizadeh, MD, PhD, assistant professor of medicine and the senior author of the paper. “Each of these steps has limitations.”

Decades ago, Stanford researchers were among the world’s leaders in developing a method for analyzing cells called flow cytometry. With this method, tissues are first separated into individual cells and exposed to fluorescently labeled antibodies that attach to particular cell surface markers. Then a few cells at a time, in tiny drops of water, are passed in front of a laser that excites the fluorescent antibodies and an
optic sensor that counts each type of cell in the drop. In some machines, the different kinds of cells can be sorted into various containers. Can you take a tissue, blend it up, look at the contents and tell what kinds of cells they came from? The standard method of cell sorting requires breaking up tissues, or disaggregating them, into individual cells, Alizadeh said. This is a rough process that destroys certain cell types and renders some tissues useless for study. In addition, the traditional method of preserving medical samples makes it impossible to process them in this way, he noted. Also, fluorescently labeled antibodies must be produced for each specific cell protein in which the scientists are interested. Antibodies may not be available for some proteins, he said.

The solution the researchers came up with is to sort not the cells, but their contents. “We were asking, ‘Can you take a tissue, blend it up, look at the contents and tell what kinds of cells they came from?’” Alizadeh said.

In developing the new method, Alizadeh and his colleagues focused not on the protein cell surface markers, but on the RNA on which those proteins were patterned. Postdoctoral scholar Aaron Newman, PhD, devised a computer algorithm to reconstruct the type and number of original cells based on the RNA contents of the mixture of all the cells.

“It’s like reconstructing a smoothie,” said Newman, a lead author of the paper. “You know it has a lot of different kinds of fruit in it, but you don’t know right away how many of each type. However, you might know that strawberries had a certain amount of sugar and red coloring, while oranges have a different amount of sugar, orange coloring and more tartness. If you analyze each of these qualities, you can reconstruct how many of each kind of fruit went into making the smoothie.”

In addition to avoiding the problems inherent in breaking up tissues into single cells, researchers using this method won’t need fluorescently labeled antibodies for the cell surface markers they are looking for, he said.

If we apply Cibersort to cancer tissues, we think we will be able to see amazing things.

Some of the most exciting recent advances in the treatment of cancer involve the use of novel drugs that engage immune responses in patients to fight the disease. These drugs often target rare and dormant populations of immune cells that reside within tumors. While some of these drugs can be dramatically effective for patients with very different tumor types, not every patient benefits equally, and some tumor types appear not to respond to these new immune therapies.

“A significant, ongoing effort is to find which immune cells mediate response and resistance to these drugs, to allow their more directed and precise use in a personalized fashion,” said Alizadeh, who is also a member of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Stanford Cancer Institute. “If we apply Cibersort to cancer tissues, we think we will be able to see amazing things.”

If the researchers apply Cibersort to old tumor samples from patients whose clinical history is known, they may be able to learn what kinds of cells signal more or less deadly cancers. They may also learn what kinds of treatments work better or worse in various subtypes of cancer. This sort of information might be most important for the antibody cancer therapies.

“There are early hints that it is very important to know about the presence of specific types of immune cells in the tumor before and after certain therapies are given, and how those cells change over time,” Alizadeh said.

Scientists discover how to change human leukemia cells into harmless immune cells

Researchers at the Stanford University School of Medicine have discovered that when a certain aggressive leukemia is causing havoc in the body, the solution may be to force the cancer cells to grow up and behave.

After a chance observation in the lab, the researchers found a method that can cause dangerous leukemia cells to mature into harmless immune cells known as macrophages.

B-cell acute lymphoblastic leukemia with a mutation called the Philadelphia chromosome is a particularly aggressive cancer with poor outcomes, said Ravi Majeti, MD, PhD, an assistant professor of medicine
and senior author of the paper. So finding potential treatments is particularly exciting. Majeti and his colleagues made the key observation after collecting leukemia cells from a patient and trying to keep the cells alive in a culture plate. “We were throwing everything at them to help them survive,” said Majeti, who is also a member of the Stanford Cancer Institute and the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Postdoctoral scholar Scott McClellan, MD, PhD, a lead author of the paper, mentioned that some of the cancer cells in culture were changing shape and size into what looked like macrophages. Majeti concurred with that observation, but the reasons for the changed cells were a mystery until he remembered an old research paper, which showed that early B-cell mouse progenitor cells could be forced to become macrophages when exposed to certain transcription factors — proteins that bind to certain DNA sequences.

“B-cell leukemia cells are in many ways progenitor cells that are forced to stay in an immature state,” Majeti said. So he, McClellan and student Christopher Dove, an MD/PhD student and the paper’s other lead author, did more experiments and confirmed that methods shown to have altered the fate of the mouse progenitor cells years ago could be used to transform these human cancer cells into macrophages, which can engulf and digest cancer cells and pathogens.

Majeti and his colleagues have some reason to hope that when the cancer cells become macrophages they will not only be neutralized, but may actually assist in fighting the cancer. Like a bloodhound owner who gives the dog a sniff of an object that was associated with the person or animal he wants to track, macrophage cells present recognizable bits of abnormal cells to other immune cells so that they can launch an attack. “Because the macrophage cells came from the cancer cells, they will already carry with them the chemical signals that will identify the cancer cells, making an immune attack against the cancer more likely,” Majeti said.

The researchers’ next steps will be to see if they can find a drug that will prompt the same reaction and that could serve as the basis for a therapy for the leukemia. There is some precedent for such a treatment. Retinoic acid is commonly used to treat another cancer called acute promyelocytic leukemia.
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. Learning how these tissue-specific stem cells operate will help us bolster our natural regenerative abilities.
Researchers isolate stem cell that gives rise to bones, cartilage in mice

Researchers at the Stanford University School of Medicine have discovered the stem cell in mice that gives rise to bone, cartilage and a key part of bone marrow called the stroma.

In addition, the researchers have charted the chemical signals that can create skeletal stem cells and steer their development into each of these specific tissues. The discovery sets the stage for a wide range of potential therapies for skeletal disorders such as bone fractures, brittle bones, osteosarcoma or damaged cartilage.

“Millions of times a year, orthopedic surgeons see torn cartilage in a joint and have to take it out because cartilage doesn’t heal well, but that lack of cartilage predisposes the patient to arthritis down the road,” said Michael Longaker, MD, a professor of plastic and reconstructive surgery at Stanford and a senior author of the paper. “This research raises the possibility that we can create new skeletal stem cells from patients’ own tissues and use them to grow new cartilage.” Longaker is also co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

The researchers started by focusing on groups of cells that divide rapidly at the ends of mouse bones, and then showed that these collections of cells could form all parts of bone: the bone itself, cartilage and the stroma — the spongy tissue at the center of bones that helps hematopoietic stem cells turn into blood and immune cells. Through extensive effort, they then identified a single type of cell that could, by itself, form all these elements of the skeleton.

Postdoctoral scholar Charles Chan says the discovery may eventually allow fat cells to be reprogrammed to become skeletal stem cells.

The scientists then went much further, mapping the developmental tree of skeletal stem cells to track exactly how they changed into intermediate progenitor cells and eventually each type of skeletal tissue.

“Mapping the tree led to an in-depth understanding of all the genetic switches that have to be flipped in order to give rise to more specific progenitors and eventually highly specialized cells,” said postdoctoral scholar Charles Chan, PhD. With that information, the researchers were able to find factors that, when provided in the right amount and at the right time, would steer the development of skeletal stem cells into bone, cartilage or stromal cells.

“If this is translated into humans, we then have a way to isolate skeletal stem cells and rescue cartilage from wear and tear or aging, repair bones that have nonhealing fractures and renew the bone marrow niche in those who have had it damaged in one way or another,” said institute director Irving Weissman, MD.

Now that the researchers have successfully mapped the skeletal stem cell system in mice, they are

Finding the cells that heal bone

In addition to finding the mouse skeletal stem cell, Michael Longaker, MD and his colleagues also found a specialized mouse progenitor cell that is activated to heal broken bones.

“We found that this is actually a different cell than the one that the body uses to maintain the bone,” Longaker says. Understanding the differences between these cells might in the future allow clinicians to activate the cells that assist bone healing.

“This is especially important in people that have conditions which inhibit bone healing, like osteoporosis or diabetes,” says Charles Chan, PhD, who also contributed to the research.

The paper is also notable because the first author is a former Stanford and NFL football who “has more experience breaking bones than healing them,” Longaker says. Owen Marecic was an All-American football player who would sometimes play both offense and defense during the same game at Stanford. For a time he played for the Cleveland Browns and the San Francisco 49ers, but ultimately decided to go back to college in preparation to go to medical school. Ultimately, Marecic hopes to become an orthopedic surgeon.

Owen Marecic
confident that they will be able to do the same in humans. “In this research we now have a Rosetta stone that should help find the human skeletal stem cells and decode the chemical language they use to steer their development,” Chan said. “The pathways in humans should be very similar and share many of the major genes used in the mouse skeletal system.”

Researchers discover that adult kidneys constantly grow and remodel themselves

Researchers at the Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Sheba Medical Center, Sackler School of Medicine in Israel have shown how the kidneys constantly grow and have a surprising ability to regenerate themselves, overturning decades of accepted wisdom that such regeneration didn’t happen and opening a path toward new ways of repairing and even growing kidneys. The researchers published their findings on May 15, 2014 in the journal Cell Reports.

“These are basic findings that have direct implications for kidney disease and kidney regeneration,” says Yuval Rinkevich, PhD, the first author of the paper and a postdoctoral scholar at the institute.

It has long been thought that the kidney cells didn’t reproduce much once the organ was fully formed. The new research shows that the kidneys are regenerating and repairing themselves throughout life. “This research tells us that the kidney is in no way a static organ,” says Benjamin Dekel, MD, PhD, a co-senior author of the paper and head of the Pediatric Stem Cell Research Institute and director of Division of Pediatric Nephrology at the Sheba Medical Center in Israel. “The kidney, incredibly, rejuvenates itself and continues to generate specialized kidney cells all the time.” Irv Weissman, MD, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, is the other co-senior author.

The research, which was done in mice, also shows how the kidney regenerates itself. Instead of a single kidney stem cell that can replace lost or damaged kidney tissue, single cells that reside in different segments of the kidney operate as kidney-forming cells to give rise to new cells within each kidney compartment. ”It’s like a tree with branches in which each branch takes care of its own growth instead of being dependent on the trunk,” Dekel says. The scientists also showed that the decision that these cells make to grow is made through the activation of a cellular pathway involving a protein called wnt. Even though populations of kidney epithelial cells look the same, the most robust kidney-forming capacity can be traced back to precursor cells in which Wnt is activated and that can only grow into certain types of specialized kidney tissue,” Rinkevich says.

“The realization that wnt signaling is responsible for the growth of new kidney tissue offers a therapeutic target to promote or restore the regenerative capacity of the kidneys,” Rinkevich says. “We may be able to turn on the Wnt pathway to generate new kidney-forming cells.”

This knowledge is extremely important to our attempts to create kidney parts in the lab at some point in the future, they say. First of all, it tells that the adult kidney is an excellent source from which to extract cells and exploit their kidney-forming capacities to build specific renal structures outside of our body. “To grow a whole kidney in the laboratory would be complicated because we would need to orchestrate the activities of many different kinds of precursor cells using just the right stimuli,” Dekel says. “It’s not like the blood and immune system, which can be reconstituted from one type of stem cell.”

Stem cells from some infertile men form germ cells when transplanted into mice

Stem cells made from the skin of adult, infertile men yield primordial germ cells — cells that normally become sperm — when transplanted into the reproductive system of mice, according to researchers at the Stanford University School of Medicine and Montana State University. The infertile men in the study each had a type of genetic mutation that prevented them from making mature sperm — a condition called azoospermia. The research suggests that the men with azoospermia...
may have had germ cells at some point in their early lives, but lost them as they matured to adulthood. Although the researchers were able to create primordial germ cells from the infertile men, their stem cells made far fewer of these sperm progenitors than did stem cells from men without the mutations. The research provides a useful, much-needed model to study the earliest steps of human reproduction.

“We saw better germ-cell differentiation in this transplantation model than we’ve ever seen,” said Renee Reijo Pera, PhD, former director of Stanford’s Center for Human Embryonic Stem Cell Research and Education. “We were amazed by the efficiency. Our dream is to use this model to make a genetic map of human germ-cell differentiation, including some of the very earliest stages.”

Reijo Pera, who is now a professor of cell biology and neurosciences at Montana State University, is the senior author of a paper describing the research. The experiments in the study were conducted at Stanford, and Stanford postdoctoral scholar Cyril Ramathal, PhD, is the lead author of the paper.

Stark differences were seen when stem cells from the fertile and infertile men were compared. The researchers estimated that the cells from the infertile men, who each had a mutation in a region of the genome known as AZF1, were about 50- to 100-fold less efficient than fertile men in their ability to form primordial germ cells.

“Studying why this is the case will help us understand where the problems are for these men and hopefully find ways to overcome them,” said Reijo Pera.

“In addition, it provides very intriguing possibilities for men rendered sterile after cancer treatments,” said Eisenberg. “Being able to efficiently convert skin cells into sperm would allow this group to become biologic fathers. Infertility is one of the most common and devastating complications of cancer treatments, especially for young boys and men.”

Cell type responsible for scarring is identified

A skin cell responsible for scarring, and a molecule that inhibits the cell’s activity, have been identified by researchers at the institute. The molecule slows wound healing in mice but alleviates scarring, the researchers said. The researchers also found that the cell may play a role in the growth of melanoma and in skin damage caused by radiation. A drug that acts in the same way as the inhibitory molecule is already approved for use in humans as a treatment for type-2 diabetes, so it could potentially move quickly into clinical trials for the treatment of scarring and melanoma.

“The biomedical burden of scarring is enormous,” said institute co-director Michael Longaker, MD, “About 80 million incisions a year in this country heal with a scar, and that’s just on the skin alone. Internal scarring is responsible for many medical conditions, including liver cirrhosis, pulmonary fibrosis, intestinal adhesions and even the damage left behind after a heart attack.”

Longaker, a professor of surgery, and institute director Irving Weissman, MD, are the senior authors on the paper, which was published in Science. Postdoctoral scholar Yuval Rinkevich, PhD, and graduate student Graham Walmsley share lead authorship.

Scars are comprised mainly of collagen, a fibrous protein secreted by a type of cell found in the skin called a fibroblast. Collagen is one of the main components of the extracellular matrix — a three-dimensional web that supports and stabilizes the cells in the skin.

Twenty-five years ago, Longaker observed that prior to the third trimester of pregnancy, human fetuses heal without scarring after surgery. Furthermore, many animals heal without scarring.

“We are the only species that heal with a pathological scar, called a keloid, which can overgrow the site of the original wound,” said Longaker. “Humans are a tight-skinned species, and scarring is a late evolutionary event that probably arose in response to a need, as hunter-gatherers, to heal quickly to avoid infection or detection by predators. We’ve evolved for speedy repair.”

In late 2013, a study led by researchers at King’s College London showed that fibroblasts in the skin of mice arise as two distinct lineages. One, in the lower layer of the skin, mediates the initial steps of repair in response to wounding.

Longaker, Rinkevich and Walmsley wondered whether this fibroblast type, which expresses a protein called engrailed, could be responsible for the collagen deposition that leads to scarring. They
generated genetically engineered mice in which the cells, called EPF cells for “engrailed-positive fibroblasts,” were labeled with green fluorescent protein to allow tracking of the cells’ location during the animals’ development. The cells were also engineered to carry a “kill switch” that could be activated by the presence of the diphtheria toxin, which would allow the researchers to assess how wounds healed in the absence of EPF cells. The researchers found that the proportion of EPF cells, compared to the overall number of fibroblasts in the skin on the backs of the animals, increased dramatically from less than 1 percent in 10-day-old embryos to about 75 percent in mice that were 1 month old.

The researchers also found evidence pointing to a major role for EPF cells in scarring. After diphtheria toxin was applied to wounds on the backs of mice, the wounds healed with less scarring. “The EPF cells are clearly responsible for the vast majority of scarring,” said Longaker. Complete healing in the diphtheria-toxin-treated wounds required an additional six days compared to controls, but much of the repaired skin looked and appeared to function normally. In contrast, scarred skin is frequently less flexible and weaker than uninjured skin.

When the researchers analyzed the EPF cells more closely, they found that they express a protein called CD26 on their surface. CD26 activity has been implicated in the metabolism of many hormones, including insulin. The human version of the marker is a target for drugs that treat low blood sugar levels in people with type-2 diabetes.

The researchers found that a small molecule that blocks the activity of CD26 also reduced the amount of scarring in a manner similar to that seen when EPF cells were eliminated. In particular, scars that formed on wounds treated with the CD26-inhibitor covered an area of only about 5 percent of the original wound. In contrast, untreated skin formed scars that covered over 30 percent of the original wound area.

In addition to examining the role played by EPF cells in scarring, the researchers investigated skin damage caused by radiation, as well as the growth of melanoma cancer cells. Radiation therapy for cancer frequently causes damage to the skin it must pass through to reach the inside of the body. Eliminating the EPF cells in the mice also eliminated much of the fibrosis caused by radiation exposure, the researchers found. Furthermore, melanoma cancer cells transplanted onto the backs of the laboratory mice grew more slowly when EPF cells were eliminated. “I’ve been obsessed with scarring for 25 years,” said Longaker. “Now we’re bringing together the fields of wound healing and tumor development in remarkable new ways. It’s incredibly exciting.”

Pioneering myriad cures with stem cell gene therapy

This year, the world’s first established stem cell gene therapy protocol for a genetic disease was submitted for final approval to the European Medical Agency (the European equivalent of the FDA). The therapy is a single-treatment, lifetime cure for a severe combined immune deficiency (SCID), which is called the “bubble boy disease” because children must live in sterile isolation their whole lives. Its success is in large part due to the work of the institute’s co-director and newest faculty member, Maria Grazia Roncarolo, MD. Roncarolo came to the Institute for Stem Cell Biology and Regenerative Medicine in order to help build “a new era in medicine, one in which we will put healthy genes
into stem cells and transplant them into patients.” At Stanford, she is building a translational research program and bring together the expertise and techniques needed to develop and test stem cell and gene therapies that can cure diseases that have so far been incurable.

“There are about 10,000 human diseases that are caused by errors in a single gene,” Roncarolo says. “And every day we discover that diseases which we thought were acquired, like psoriasis and inflammatory bowel syndrome, turn out to be genetic.” All of these diseases are potentially addressable by stem cell gene therapies, she says. Stem cells are used in order to make gene therapy long-lasting, but Roncarolo observes that developing the capability to treat patients with stem cells also has the potential to cure many, many more diseases. “The use of patients’ purified stem cells makes gene therapy safer and more effective. In addition, we can transplant purified blood stem cells from healthy donors into patients to cure cancer and immune mediated diseases like type-1 diabetes”, she says. This also sets the stage for transplanting purified stem cells from various tissues to cure other diseases, such as using purified skeletal stem cells to regenerate damaged cartilage or purified heart stem cells to renew a failing heart. Before coming to the institute, Roncarolo was scientific director at the San Raffaele Institute in Milan, Italy. There, she developed and refined therapies to treat genetic diseases in children. Despite the fact that other researchers had experienced some well-publicized failures in treating genetic disease, she pressed on. The first SCID patient with adenosine deaminase deficiency (ADA) was successfully treated with stem cell gene therapy in 2000, and almost 50 SCID-ADA patients have been treated since then. “We restored immune function and saved patients’ organs from the effects of toxic metabolites” Roncarolo says. “We basically cured these patients.” Her team went on to conduct trials for therapies of two other deadly congenital diseases, metachromatic leukodystrophy (MLD) and Wiskott-Aldrich syndrome. “My most important contribution is that there are kids who were incurable before but now have options,” she says. “These were proof of principle studies to prove that gene therapies can cure monogenic therapies,” Roncarolo says. “The next step is to apply this knowledge to less rare diseases.” Roncarolo, who is a professor in the Stanford department of pediatrics, will be working with children in the Lucile Packard Children’s Hospital. Stanford will be building a GMP (good manufacturing practices) facility to grow and purify stem cells that can be used in human clinical trials. “We need to build the team and the infrastructure, which means the people, facilities and the know-how,” Roncarolo says. “In five years we want to have built a pipeline of stem cell therapies and have a number of clinical trials underway. We want Stanford to have a reputation as a leading center in translating discoveries into therapies.”
Embryonic stem cells naturally develop into every kind of cell in our body. Institute researchers are exploring the mysteries of how this occurs naturally, and how errors occur during the development process.

Researchers at the institute are also creating embryonic-like cells, called induced pluripotent stem (iPS) cells. They are now investigating the use of iPS cells therapeutically and for creating disease-in-a-dish models of clinical disorders.
Researcher looks at growing organs for transplantation

There are about 100,000 people on waiting lists for organ transplants in the United States. Every day, 18 of those people die still waiting for an available organ. One of the institute’s most recently recruited investigators, Hiro Nakauchi, MD, PhD, has a vision of a future in which we can grow replacement organs for many of these patients rather than waiting for an appropriate organ to become available. Furthermore, these organs will be perfectly suited for each patient because they will be tailor made to be an exact genetic match. In fact, in many ways the organ that Nakauchi grows would be your organ.

In order to be able to make organs to order, Nakauchi has embarked on a visionary research program to explore the idea of growing human organs in other animals. The way it works is this: if a patient needs a new heart, Nakauchi might create a pig embryo that is missing the gene or genes necessary for the formation of a heart. He might then take a skin cell from a patient, transform it into an embryonic-like induced pluripotent stem cell and embed that cell into the pig embryo. As the embryo grows into a pig inside a sow, only the human cells will have the necessary genes for the formation of a heart. So while most of the piglet is derived from pig cells, its heart will be formed from human cells—cells that are in fact genetically identical to the patient’s own cells. “We hope we can do this with any organ,” Nakauchi says. “As long as we can find a gene that preferentially interferes with the development of the target organ.” So far, Nakauchi has succeeded in making this scheme work in lower mammals; he has grown mouse organs in rats and vice versa. He is currently planning on continuing his experiments in larger animals.

In addition to his groundbreaking research on growing human organs in other animals, Nakauchi is embarking on other innovative projects. One of the challenges to genetic and stem cell therapy is that it often requires transplanting cells into the body. In the case of blood stem cells, the high-dose chemotherapy or radiation is necessary to remove the body’s own blood stem cells and make room for the transplanted cells. This pre-treatment is very dangerous in itself causing severe side effects, with damage to liver, kidney, heart, lung, and other major organs. This limits the number of patients who can receive such treatment. Young patients also are at risk of later effects such as secondary malignancy, endocrinopathy, growth retardation, and reproductive failure. Nakauchi is exploring gentler ways to make space in the body for the transplanted cells. He has discovered that simply by feeding mice a diet deficient in a particular amino acid, blood stem cells begin to die, while other cells in the body don’t seem to be as strongly affected. A dietary solution may eventually allow clinicians to avoid using the highly toxic treatments that have traditionally been used for blood stem cell transplant.

Nakauchi has also been researching methods for creating blood platelets, which currently can only come from donated blood and cannot be stored easily. Since platelets are important to stop bleeding, a
constant supply of those cells is critically important. In addition, he is studying ways to rejuvenate killer T cells obtained from the patients with cancer or viral infection, potentially increasing the effectiveness of immunotherapy.

Although Nakauchi’s research covers a wide territory, he says his major goal has always been the same: to translate cutting-edge findings and technologies in basic stem cell science into clinical applications. That and one other thing: just as he became the scientist he is through the mentorship of the Herzenbergs and others, Nakauchi believes that training the next generation of scientists is highly important. In fact, he has trained a large number of young scientists; many of whom are active scientists in stem cell research as well as in other fields.

Viral proteins may regulate human embryonic development

A fertilized human egg may seem like the ultimate blank slate. But within days of fertilization, the growing mass of cells activates not only human genes but also viral DNA lingering in the human genome from ancient infections.

Now researchers at the Stanford University School of Medicine have found that the early human cells produce viral proteins, and even become crowded with what appear to be assembled viral particles. These viral proteins could manipulate some of the earliest steps in human development, affecting gene expression and even possibly protecting the cells from further viral infection.

The finding raises questions as to who, or what, is really pulling the strings during human embryogenesis.

“It’s both fascinating and a little creepy,” said Joanna Wysocka, PhD, associate professor of developmental biology and of chemical and systems biology. “We’ve discovered that a specific class of viruses that invaded the human genome during recent evolution becomes reactivated in the early development of the human embryo, leading to the presence of viral-like particles and proteins in the human cells.”

A paper describing the findings was published in Nature. Wysocka is the senior author, and graduate student Edward Grow is the lead author.

Retroviruses are a class of virus that insert their DNA into the genome of the host cell for later reactivation. In this stealth mode, the virus bides its time, taking advantage of cellular DNA replication to spread to each of an infected cell’s progeny every time the cell divides. HIV is one well-known example of a retrovirus that infects humans.

When a retrovirus infects a germ cell, which makes sperm and eggs, or infects a very early-stage embryo before the germ cells have arisen, the viral DNA is passed along to future generations. Over evolutionary time, however, these viral genomes often become mutated and inactivated. About 8 percent of the human genome is made up of viral sequences left behind during past infections. Over evolutionary time, however, these viral genomes often become mutated and inactivated. About 8 percent of the human genome is made up of viral sequences left behind during past infections. One retrovirus, HERVK, however, infected humans repeatedly until relatively recently — within about 200,000 years. Much of HERVK’s genome is still snuggled, intact, in each of our cells.

Most of these sequences are inactive in mature cells, but recent research has shown that they can spring to life in tumor cells or in human embryonic stem cells. A study published recently in Cell Stem Cell by researchers from Singapore’s Genome Institute showed that sequences from a primate virus called HERVH are also activated in early human development.

Now the Stanford researchers have shown for the first time that viral proteins are abundantly present in the developing human embryo and assemble into what appear to be viral particles in electron microscopy images. By following up with additional studies in human embryonic cells grown in vitro, scientists showed that these viral proteins affect gene expression in the developing embryo and may protect the cells from infection by other viruses.
Pluripotent cells created by nuclear transfer can prompt immune reaction

Mouse cells and tissues created through nuclear transfer can be rejected by the body because of a previously unknown immune response to the cell’s mitochondria, according to a study in mice by researchers at the Stanford University School of Medicine and colleagues in Germany, England and at MIT.

The findings reveal a likely, but surmountable, hurdle if such therapies are ever used in humans, the researchers said.

Stem cell therapies hold vast potential for repairing organs and treating disease. One significant hope rests on the potential of pluripotent stem cells, which can become nearly any kind of cell in the body. One method of creating pluripotent stem cells is called somatic cell nuclear transfer, and involves taking the nucleus of an adult cell and injecting it into an egg cell from which the nucleus has been removed.

The promise of the SCNT method is that the genetic identity of the new pluripotent cell would be the same as the patient’s, since the transplanted nucleus carries the patient’s DNA,” said cardiothoracic surgeon Sonja Schrepfer, MD, PhD, a co-senior author of the study.

“The hope has been that this would eliminate the problem of the patient’s immune system attacking the pluripotent cells as foreign tissue, which is a problem with most organs and tissues when they are transplanted from one patient to another,” added Schrepfer, who is a visiting scholar at Stanford’s Cardiovascular Institute. She is also a Heisenberg Professor of the German Research Foundation at the University Heart Center in Hamburg, and at the German Center for Cardiovascular Research.

A dozen years ago, when Institute Director Irving Weissman, MD, headed a National Academies panel on SCNT cells, he raised the possibility that the immune system of a patient who received the cells might still react against proteins from the cells’ mitochondria, which act as the energy factories for the cell and have their own DNA. This reaction could occur because cells created through SCNT contain mitochondria from the egg donor and not from the patient, and therefore could still look like foreign tissue to the recipient’s immune system, said Weissman, the other co-senior author of the paper.

That hypothesis was never tested until Schrepfer and her colleagues took up the challenge. “There was a thought that because the mitochondria were on the inside of the cell, they would not be exposed to the host’s immune system,” Schrepfer said. “We found out that this was not the case.”

Schrepfer used cells that were created by transferring the nuclei of adult mouse cells into enucleated egg cells from genetically different mice. When transplanted back into the nucleus donor strain, the cells were rejected although there were only two single nucleotide substitutions in the mitochondrial DNA of these SCNT-derived cells compared to that of the nucleus donor.

“We were surprised to find that just two small differences in the mitochondrial DNA was enough to cause an immune reaction,” she said.
Irving Weissman, MD
Director
Director of the Ludwig Center for Cancer Stem Cell Research
Virginia and D.K. Ludwig Professor for Clinical Investigation and Cancer Research

Irving Weissman has directed the institute since its founding, providing 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) stems cell in mice. He subsequently found the human hematopoietic stem cell, the human neuronal stem cell, and the human leukemia stem cell. His work has opened up an entirely new area of scientific research with enormous potential for life-saving therapies.
Michael T. Longaker, MD, MBA, FACS
Co-Director
Director, Program in Regenerative Medicine
Deane P. and Louise Mitchell Professor

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

Maria-Grazia Roncarolo
Co-Director
George D. Smith Professor in Stem Cell and Regenerative Medicine

Maria Grazia Roncarolo, MD, is a world leader in stem cell and gene therapies. She is the former scientific director of the San Raffaele Scientific Institute in Milan, Italy, where she showed that gene therapy could be used effectively in treating formerly untreatable diseases. Dr. Roncarolo was recruited to lead the institute’s efforts to translate basic scientific discoveries in the field of regenerative medicine into novel patient therapies, including treatments based on stem cells and gene therapy.

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.
Working with her primary mentor, Kristy Red-Horse, PhD, and with Weissman as her secondary mentor, Volz studied stem cells in the tissue that encloses the heart, called the epicardium. In a series of experiments, she studied the pathway epicardial cells take as they migrate into the heart to form coronary artery smooth muscle cells, an important cell type that regulates the vessel diameter. She discovered progenitor cells that derive from the epicardium and can differentiate into contractile smooth muscle cells. She furthermore discovered the signals that change these progenitors into smooth muscle cells. “Understanding this cell lineage tells us about normal development, but it also can clue us into how coronary arteries develop abnormally,” Weissman says. “Katharina’s experiments open the door to understanding the heart’s regeneration following atherosclerotic closure and the atherosclerotic process itself.”

Volz was born and raised in Ulm, Germany. She attended a biotechnology high school and was the first German high school student to be accepted into a research program at Harvard University. During her undergraduate years in Molecular Biology at the University of Graz, she spent over 8500 hours in five different research labs and was given the American Heart Association undergraduate research award. As a graduate student and CIRM (California Institute for Regenerative Medicine) fellow at Stanford, she was given the SCBRM Young Investigator Award for her research.

In addition to her own scientific advancements, Volz has also been working on another project to improve the fundamental process of research. Over the last six months, Volz and classmates have been developing a system that enables scientists to easily access and engage with the most accurate and relevant research. “It’s my goal to make research and discovery faster, cheaper and leaner,” Volz says. “People’s lives and entire industries depend on the R&D pipeline. An improvement of the R&D pipeline of only by a few percent would accelerate our progress across the board.”

She has incubated these concepts through Stanford’s Startup Garage program and after graduation intends to work on this full-time at a company she founded, OccamzRazor. Volz believes her work will increase the efficiency of scholarly research.
2014 - June 2015 Publications

Ash Alizadeh


Bi-culturing of grass pea and barley in the semi-arid regions of Iran Alizadeh, K., Pooryousef, M., Kumar, S. Legume Research. 2014;37(1) Article Digital Source: Scopus: 7


Philip Beachy


Samuel Cheshier


Michael Clarke

KIT Signaling Promotes Growth of Colon Xenograft Tumors in Mice and is Upregulated in a Subset of Human Colon Cancers.


Maximilian Diehn


Tushar Desai


Michael Longaker


Nanotechnology in bone tissue engineering. Walmsley GG, McArdle A, Tevlin R, Momeni A,


Clonal analysis reveals nerve-dependent and independent roles on mammalian hind limb tissue maintenance and regeneration. Rinkevich


Reply: tension shielding with the embrace device: does it really improve scars


Stem cell labeling for delivery and tracking using noninvasive imaging 2012 CRCnetBASE Book Digital View Description Lane Catalog Source: Lane Catalog Results


Ravi Majeti


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Michelle Monje


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A comprehensive system for generation


Histone demethylase Jmjd3 is required for the development of subsets of retinal bipolar cells. Iida A, Iwagawa T, Kuribayashi H, Satoh S,


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A continuous molecular roadmap to iPSC reprogramming through progression analysis of single-cell mass cytometry. Zunder ER, Lu-


Joanna Wysocka


