2013 ANNUAL REPORT

Message from the Director

This has been an exciting year. We took several steps that bring us to the threshold of making stem cell therapies and regenerative medicine realities.

Two essential hires—of Hiromitsu Nakauchi, MD, PhD, and Maria Grazia Roncarolo, MD, PhD—were very big steps. Hiro Nakauchi was director of the Institute for Stem Cell Biology at the University of Tokyo. We were lucky enough to attract him to finish his career at Stanford. In the past several years, Hiro has come up with an innovative approach for using stem cells to build an entire organ. For instance, in mice he can establish mouse embryos that fail to have all the genes necessary to create a pancreas. When he takes rat embryonic stem cells (which do have all the genes necessary to build a pancreas), implants those cells in the mouse embryo, and then implants that embryo in a female mouse, the result is a mouse with a rat pancreas. Hiro has now found another gene necessary for kidney formation, making it possible to use a similar strategy to create a kidney.

In these cases, the pluripotent stem cells that become the target organ can be derived from embryonic stem cells, but also from reprogrammed adult tissue cells. In the distant future, one could hope that a patient's own skin cells (or other adult cells) could be reprogrammed and used as stem cell seeds that might grow into an organ that is genetically identical to the patient's own organs. That organ could then be transplanted to replace one that is missing, degenerated or deficient. This work fits well with Marius Wernig's research on transforming adult cells directly into neurons, neural precursors, and eventually neural stem cells.

Maria Grazia Roncarolo comes to us from the San Raffaele Scientific Institute in Italy. Under her directorship, the institute and its associated hospital and university became the premier clinical translation site in Europe, if not in the world. One of her many successes was in building a team that carried out the first successful genetic therapies of the blood-forming cells in humans to treat otherwise disastrous diseases.

Maria comes to Stanford as a co-director of the Institute for Stem Cell Biology and Regenerative Medicine. She also becomes the chief of the Division of Pediatric Translational and Regenerative Medicine within the Department of Pediatrics. She is in charge of developing the clinical stem cell program at Stanford, which will hopefully be funded by CIRM.

She will help us establish both purified blood forming stem cell therapies and also gene modification of patients' own blood-forming stem cells.

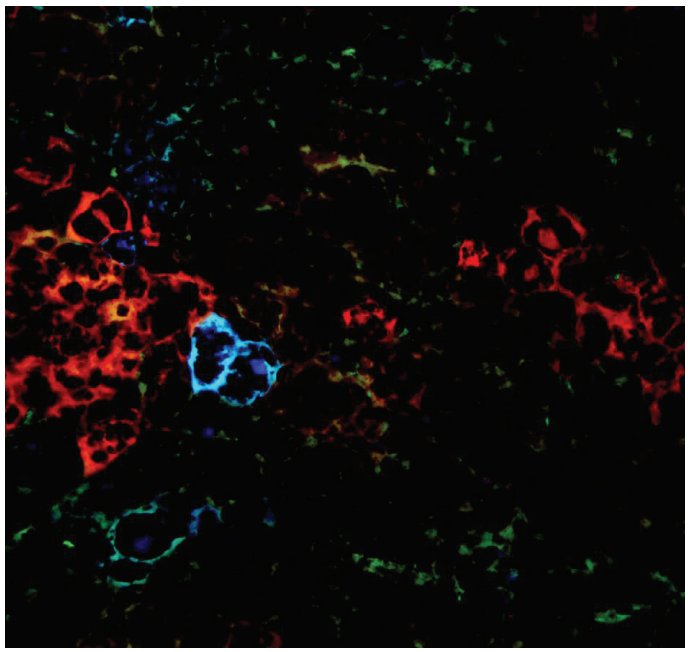
In addition, she has a program in which she can expand and transplant the kinds of T lymphocytes that regulate and suppress rather than activate dangerous immune responses. She hopes that this will provide both mechanisms for inducing transplantation tolerance and overcoming autoimmune diseases such as inflammatory bowel disease and ulcerative colitis.

We continue to press forward with the clinical trials of the anti-CD47 antibody, which we hope will soon prove to be a potent anti-cancer agent. The trial and the therapy are new in several ways. For one thing, this clinical trial is being done by Stanford (with funding from the California Institute for Regenerative Medicine), without a commercial sponsor and the distorting financial incentives that are an inevitable part of these arrangements. In addition, the antibody seems to

subvert a mechanism that nearly all cancers use to evade the immune system, so it may potentially be part of a universal cancer therapy. Researchers also showed that a high-affinity version of the SIRP-alpha molecule (that natural CD47 receptor target) could also be used to confound the same protective mechanism on cancer.

In the last year, we showed that the anti-CD47 antibody not only recruits macrophages to help eliminate the tumor, but we have found that these macrophages break down tumor proteins and present them to Killer T cells. This opens possibilities that we will find such activated, anti-tumor killer T cells in patients. If so, then the therapy is acting as a kind of anti-cancer vaccine, a possibility that is obviously exciting. One more exciting element of this clinical trial is that we will be testing another dramatic discovery by institute scientists Max Diehn and Ash Alizadeh, who have developed a highly sensitive method of detecting cancer DNA in the bloodstream. Cancer cells naturally release mutated DNA into the bloodstream, but when macrophages consume cancer cells they completely degrade the DNA and don't release it into the bloodstream. Therefore, the loss of cancer DNA in the bloodstream may be an early sign of therapeutic success in patients treated with anti-CD47 antibody. Max and Ash's work may lead not only to a powerful diagnostic and therapeutic tool for all sorts of cancers, but may ultimately become a way to screen for cancer simply by analyzing a blood sample.

In concert with the Stanford Cancer Institute, the ISCBRM is recruiting cancer specialists who will use the transfer of T cells to treat cancers. This fits with the longstanding interest of Stanford researcher Ronald Levy in vaccinating patients against their own cancers. The efforts of the CD47 team can reveal new T cells against each of the cancers being treated, and this too should serve as a foundation for T cell oncologists to develop



therapies. Hiro Nakauchi has found that he can reprogram killer T cells to embryonic stem cells, which he then converts to more T cells with the same immune specificity. We hope that in the coming years, these too will be the source of new anti-cancer therapies.

This year, institute researchers have made a number of discoveries in what might be called foundational stem cell science, although many of these "basic" findings suggest immediate applications in the clinic. Mike Clarke's lab was the source of the discovery that Down syndrome is largely a stem cell disease—many of the symptoms of Down syndrome can be traced to the excess production of a molecule that regulates stem cell growth. Marius Wernig's lab revealed

a method for converting skin cells directly into precursors for oligodendrocytes—the cells that sheath neurons and which are attacked in many neurological disorders.

Mike Longaker and his colleagues have been hard at work tracking down the stem cell that produces bone, blood and immune cells, and the stromal cells that guide the development of various cell types. This research is already leading to clinical advances in bone cancer and bone regeneration.

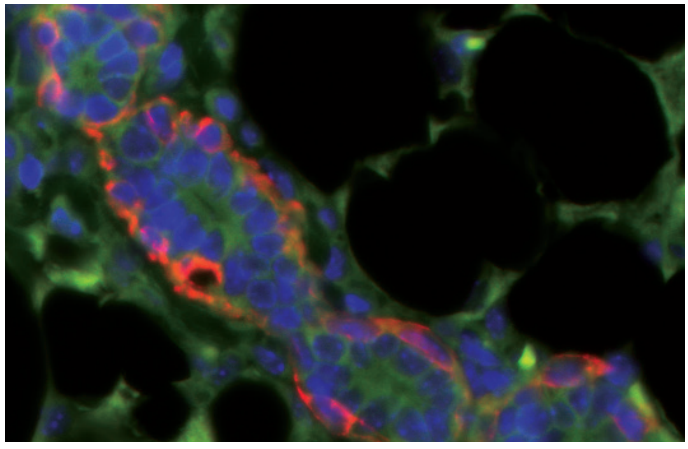
This year, Phil Beachy published significant research showing that in both bladder cancer and bladder inflammation there is cross-talk between hedgehog signalling pathways. These finding are allowing Phil to track down the steps between normal bladder stem cells and bladder cancer stem cells.

Roel Nusse is using new tools to study the wnt signaling pathway to demonstrate that both skin and liver development include stem cells driven by the wnt pathway. Because the wnt pathway is often hijacked in breast cancer and skin cancer and in some leukemias, his laboratory is involved in a two-step process, not only studying how the wnt pathway operates in regenerative cells, but also looking for inhibitors of the wnt pathway that might check the reproduction of cancer stem cells.

These are just a few of the promising developments that institute scientists have been engaged in over the course of the year. The year 2013 was a critical step on the way to the new clinical trials and new translational applications of Stanford stem cell science that are coming soon.

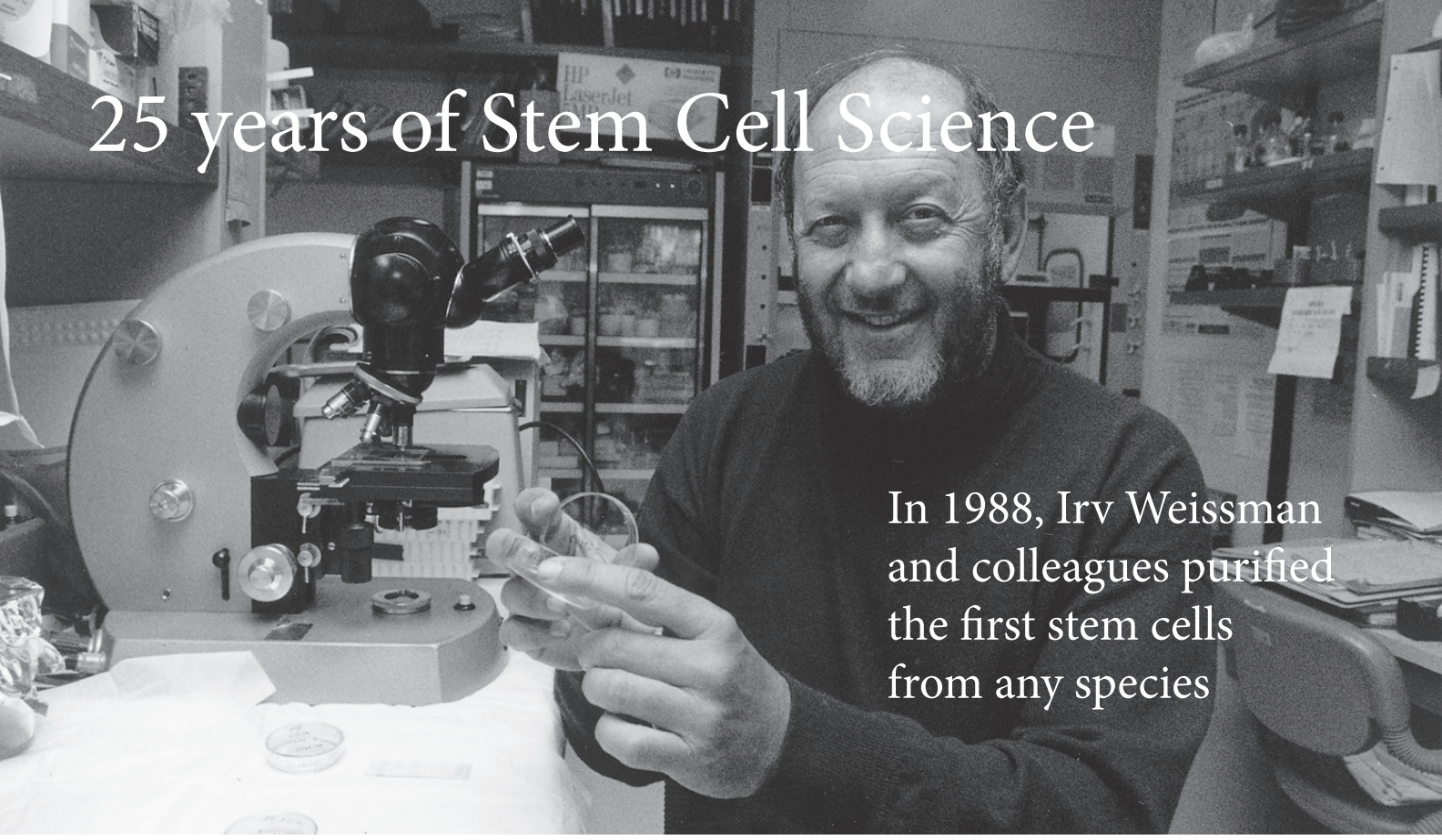
The ISCBRM has now filled out most of its faculty slots. The basic scientists and faculty in the clinical subspecialties are moving Stanford toward being a site of discovery up to, and through, clinical trials, usually without involving financing from commercial entities.

On the cancer side, we have greatly added funding from the Ludwig Foundation. On the regenerative side, our funding has been primarily from the California Institute for Regenerative Medicine. In addition, we have a core of committed donors whose view of the future of medicine coincides



with ours. If we are successful in this revolution, if we can translate stem cell discoveries to therapies, then instead of using small molecules or daily therapeutics we can look forward to treatments that are given one time and are effective for life. Although these therapies may seem expensive now, in the long run they would be more cost effective and could go a long way to reducing health care costs.

25 years of Stem Cell Science



In 1988, Irv Weissman and colleagues purified the first stem cells from any species

In 1988, institute director Irv Weissman published a paper documenting the identification and purification of the mouse blood stem cell. This was the first time that any stem cell (other than embryonic stem cells) from any species had been identified and isolated in such a concentrated form. The publication of that paper in the July 1, 1988 issue of the journal Science in many ways marked the beginning of a new era in stem cell research and medicine.

Stem cells are very rare. Among a sample of serum isolated from the bone marrow, only about 1 in 10,000 to 20,000 cells are true hematopoietic (blood) stem cells (HSCs). Before the Weissman lab's work, other researchers had begun to increase the concentration of related cells, but they had not yet purified stem cells themselves. To prove that they had isolated stem cells, the researchers showed that their purified cells could not only reproduce, but could also generate all blood cell types.

The 1988 Science paper was also a landmark in that Weissman and his colleagues developed novel assays to show the full regeneration of all blood cell types, developed new techniques for purifying stem cells and provided the most accurate description yet of the particular cell-surface markers that defined HSCs. "The 1988 Science article extended previous work by defining a broadly applicable approach to the identification and isolation of mouse HSC, and by establishing a new transplant model," says Gerald Spangrude, who was first author on the 1988 paper and is now a professor at the University of Utah School of Medicine. The Weissman lab established a robust model system for analysis of HSC that still persists 25 years later, he says. "Virtually every modern study of mouse HSC biology in the literature today utilizes some or all of the innovations introduced by the landmark 1988 study."

After the 1988 Science paper, Weissman and his colleagues went on to identify and purify human HSCs as well as stem cells for many other kinds of tissues in humans as well as animals. These discoveries set the stage for stem cell-based therapies of intractable diseases such as leukemia, breast cancer, spinal cord injury, neurodegenerative disease, autoimmune disease and immunodefficiencies.

Research

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 propogates.

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.

CD47

Clinical Trials of Anti-CD47 Antibody as a Cancer Therapeutic

All types of cancer seem to carry excess amounts of a cell surface protein (CD47) that protects the cancer from the patient's immune system. The Stanford Group, led by Ravi Majeti, MD, PhD, an assistant professor in the institute, and Irv Weissman, MD, found that CD47 is a "don't eat me" signal to immune cells called macrophages. Macrophages bind to cells that are damaged or bear the kinds of mutations that lead to the cells to initiate a cell death program. Before the damaged cells die, they express cell-surface 'eat me' signals recognized by scavenger macrophages. Incipient cancer cells eventually defeat programmed cell death by further mutations, and they defeat the "eat me" signals for programmed cell removal by expressing the dominant "don't eat me" signal CD47.

Blocking the CD47 signal from human cancers transplanted into mice effectively reduces or eliminates the solid tumors or blood cancers. The use of specialized antibodies to block the CD47 signal is also a powerful anticancer therapy when combined with other antibodies that have already been approved as anti-cancer therapies.

Many scientists within and outside of the institute have spent 2013 preparing for clinical trials of the anti-CD47 antibody in humans. The trials are highly unusual in that they will be organized, sponsored and conducted by Stanford University (and in the United Kingdom by governmental organizations), independent of any commercial pharmaceutical company.

Ravi Majeti, MD, PhD

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.

CD47 and cancer vaccines

This year, researchers at the institute showed that the use of anti-CD47 antibodies, which are known to fight cancer via immune cells called macrophages, also prompts the disease-fighting killer T cells to attack the cancer. The research opens the door for potentially creating custom cancer vaccines.
In the past, researchers have tried to create cancer vaccines by presenting fragments (antigens) of cancers to T cells with the hope that the sensitized T cells would activate the immune system to attack the cancer. But the techniques used in the past only modestly activated the potent immune cells, called Killer T cells.

Irv Weissman, MD

Irv Weissman, MD, and his colleagues discovered that when anti-CD47 antibodies prompt macrophages to engulf and devour cancer cells, the macrophages become very good at presenting pieces of the cancer to T cells and are effective at activating the Killer T cells to attack cancer. The strategy of using macrophages to sensitize T cells to cancers offers a whole new route for directing the immune system to attack cancers.
The research also renews interest in macrophage cells as antigen presenters. For years, researchers have focused on another cell, called the dendritic cell, as the most important antigen presenter to T cells.

SIRP-alpha: turning anti-cancer bullets into guided missiles

Building on previous research showing that cancer cells send signals to the immune system to avoid being attacked, Stanford scientists have engineered new molecules that are highly proficient at neutralizing those signals, allowing the immune system to efficiently kill cancer cells. The molecules dramatically increase the effectiveness of certain existing cancer therapies and may open up other avenues for treating cancer using patients' own immune systems.

Stanford researchers have previously shown that CD47, a molecule found on the surface of many cancers, acts as a "don't eat me" signal that protects the cancer from roving immune cells called macrophages. When this signal is blocked with antibodies, macrophages engulf and destroyed the cancer cells.
More recently, Stanford scientists wondered if they could engineer molecules that block the "don't eat me" signal more effectively. They began by modifying a protein called SIRP-alpha, which is found on macrophages and is the natural receptor for CD47. Stanford researchers Aaron Ring, PhD and Kipp Weiskopf, MD/PhD students at the time, with their PhD advisors Chris Garcia and Irv Weissman, then engineered new versions of SIRP-alpha that bind 50,000 times more strongly to CD47 than the natural version of the molecule, making them extremely potent blockers of the "don't eat me" signal.
But the researchers found blocking the CD47 "don't

eat me" signal is not, by itself, enough to stimulate macrophages to attack cancer cells. Instead, the group demonstrated that blocking CD47 boosts the activity of macrophages when a second "eat me" signal is provided. This signal can be provided by certain anti-cancer antibody therapeutics, many of which are already approved by the FDA and in use clinically. These findings have tremendous therapeutic implications, because the high-affinity SIRP-alpha molecules could selectively boost the destruction of cancer cells by these antibody therapies, without increasing toxic side effects such as the destruction of healthy, non-cancerous cells.

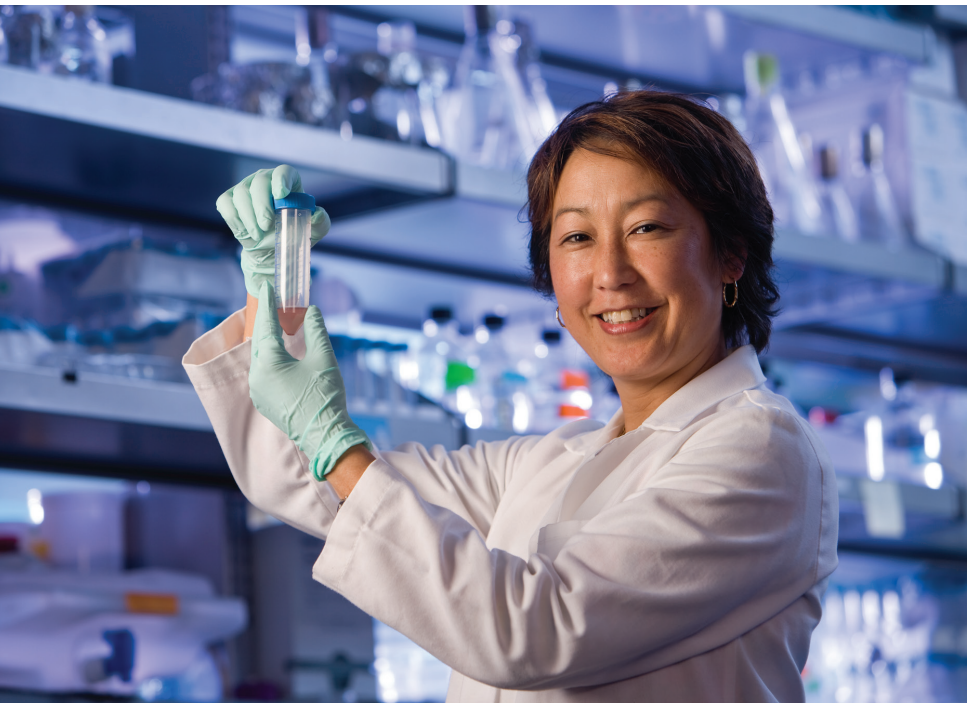
Clinical trials for use of purified stem cells in the treatment of metastatic breast cancer

Institute researcher Judy Shizuru, MD, PhD and colleagues are moving forward with plans to conduct clinical trials of a technique to use high-dose chemotherapy and purified blood-forming stem cells to treat metastatic breast cancer.

Shizuru's plans for a new clinical trial of the technique follow encouraging results from a follow-up study of the patients who took part in a much smaller clinical trial of the technique 15 years ago. This was a time when much of the rest of the world was trying to treat metastatic breast cancer with high-dose chemotherapy (which killed the blood-forming stem cells as well as the cancer cells), followed by mobilized blood transplantation to rescue the blood-forming system. The problem was that mobilized blood taken from the patient and given back to the same patient after chemotherapy often carried cancer stem cells too. Physicians were giving patients back their own cancer. Stanford was the only place in the world where the patients' blood-forming system was rescued using purified stem cells which were free of cancer.

In the follow up study, 33% of patients treated at Stanford for metastatic breast cancer using high-dose chemotherapy and purified stem cell transplantation were still alive 15 years later, most of them with no signs of cancer. This is in contrast to a 9% long-term survival rate (7% with no signs of cancer) for stage IV breast cancer patients given standard-of-care therapy.

Judith Shizuru, MD, PhD



Catching cancer DNA in blood samples

Knowing whether a cancer is dead, dying or hiding is often difficult for phsyicians looking at radiographic films. Radiation therapy can leave scarring that may look like tumor tissue but hold no cancer. Conversely, images may be clear, indicating that a cancer is gone, but not be able to show the few cancer cells that remain and that will later cause a relapse.

At the institute, Max Diehn, MD, PhD, Ash Alizadeh, PhD, Aaron Newman, PhD, and their colleagues have recently discovered a method of monitoring cancers by detecting cancer DNA in the blood. When cancer cells die, they release their DNA into the bloodstream. Finding that DNA and identifying the key mutations that indicate that the DNA came from a cancer cell allows physicians to know if cancer is gone or if it is just hiding and waiting for the chance to come back at a later date.

The technology also will let doctors

Maximilian Diehn, MD, PhD

know fairly quickly whether a new treatment is working or not. Currently, patients may have to undergo weeks of chemotherapy before images can reveal if their tumors are shrinking or not.

The technique also offers the promise of getting a "blood-borne biopsy" of the cancer. Because cancer tumors get new mutations all the time, it's important to keep track of what new mutations are arising. This information can give physicians insights into what the cancer is doing and what targeted therapies might be useful. Most biopsies are highly invasive, often requiring surgery to reach tumors that are deep in the body. The recently developed technique offers doctors the ability to monitor these genetic changes without performing a surgical biopsy, through a simple blood test.

The new technology is more than 100 times more sensitive than previous tests for DNA in the blood. This level of sensitivity may allow researchers to create at last what has been a longtime dream: a simple blood test to screen people for cancer.

Researchers show that approved drugs target breast cancer stem cells, perhaps leading to wider use against more tumors

Trials of anti-HER-2 agents like Herceptin in metastatic patients with HER-2-negative tumors haven't shown tumor shrinkage or improved outcomes, which is why these drugs are only approved for use in HER-2 positive tumors. However, more recent clinical analyses have indicated that patients with microscopic disease remaining after treatment for earlier stage disease may see improved survival from anti-HER-2 agents regardless of their HER-2 status. Max Diehn, MD, PhD, a member of the institute, hypothesized that although anti-HER-2 agents weren't harming the majority of breast cancer cells in a HER-2-negative tumor, they were targeting a small population of the most important cells—cancer stem cells. If the cancer stem cells in a tumor can be killed, the rest of the tumor cells will die or be killed off by the body's immune system over time. Killing the breast cancer stem cells can also keep the cancer from spreading to other organs.

The researchers think that this is the first time that a cancer drug found to be ineffective for a population of patients was actually found to be beneficial when reexamined in light of its specific effect on cancer stem cells.

Stem cell research uncovers new anti-cancer power in old drug

Institute researchers have long been studying the stem cell pathways involved in wound healing, a process that activates stem cells to replace damaged tissue. One major theory of cancer is that some cancers are the result of an inappropriate activation of these wound healing pathways, leading to the unregulated cell growth that typifies the disease. A team led by institute scientist Phil Beachy, PhD, focused on the Hedgehog pathway, which is important in both wound healing and in development, and found that blocking that molecular pathway can inhibit the growth of some cancers. He then initiated a search for existing drugs that blocked the hedgehog pathway and found Itraconazole, a drug that had previously been approved by the FDA as an antifungal agent.

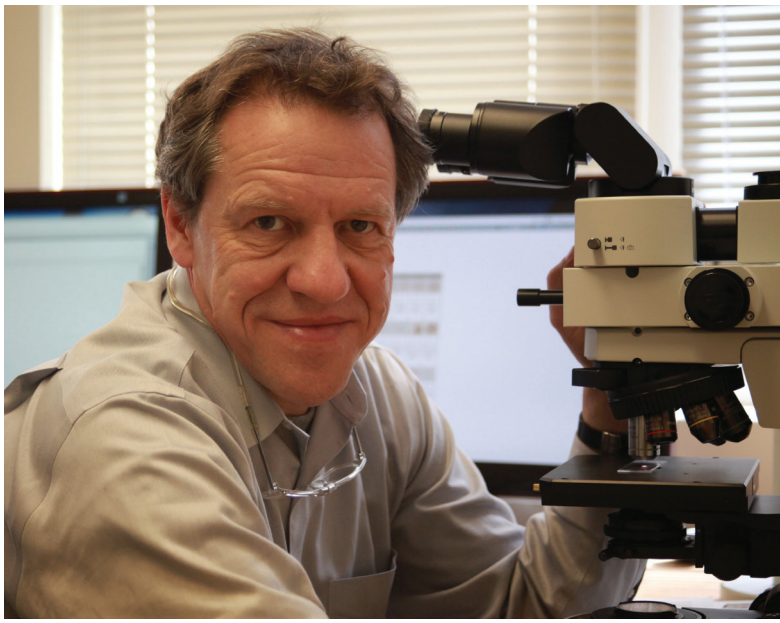
Philip Beachy, PhD

A clinical trial of Itraconazole at Stanford this year demonstrated that it is effective in shrinking basal cell carcinoma, which is the most common form of skin cancer.

Antibody hinders growth of Gleevec-resistant gastrointestinal tumors

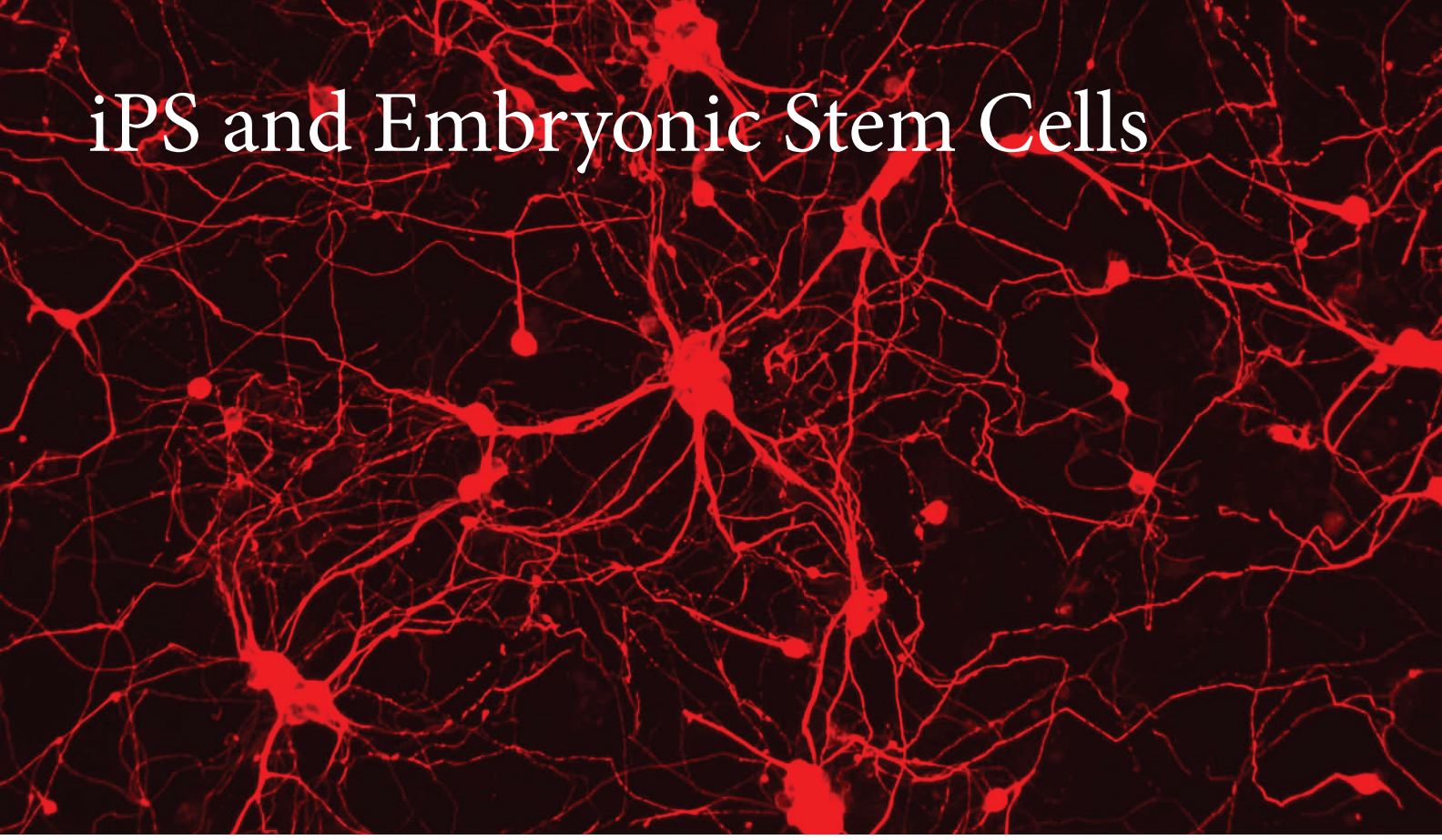
Institute researchers Matt van de Rijn, MD, and Irv Weissman, MD, working with research fellows Badre Edris and Jens Peter Volkmer, found that an antibody that binds to a molecule on the surface of a rare but deadly tumor of the gastrointestinal tract inhibits the growth of the cancer cells in mice.

The effect remains even when the cancer cells have become resistant to other treatments, and the findings may one day provide a glimmer of hope for people with the cancer, known as gastrointestinal stromal tumor, or GIST. The scientists hope to move into human clinical trials of the antibody within two years, and have dedicated their research to the memory of Angela Lee, PhD, an institute employee who recently died of that disease.



Matthew van de Rijn, MD

The antibody's target is a receptor called KIT, which is often mutated in patients with the cancer. When mutated, KIT sends a continuous stream of messages, telling the cell to grow uncontrollably. The Stanford researchers found that the antibody reduces or inactivates the amount of KIT on the surface of the cancer cells and stimulates immune cells called macrophages to kill the rogue cells.



iPS and Embryonic Stem Cells

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.

Researchers turn skin cells directly into the cells that insulate neurons

Researchers at the institute have succeeded in transforming skin cells directly into precursor cells for oligodendrocytes, the cells that wrap nerve cells in the insulating myelin sheaths and help nerve signals propagate. The current research was done in mice and rats. If the approach also works with human cells, it could eventually lead to cell therapies for diseases like inherited leukodystrophies — disorders of the brain's white matter — and multiple sclerosis, as well as spinal cord injuries.

Without myelin to insulate neurons, signals sent down nerve cell axons quickly lose power. Diseases that attack myelin, such as multiple sclerosis, result in nerve signals that are not as efficient and cannot travel as far as they should. Myelin disorders can affect nerve signal transmission in the brain and spinal cord, leading to cognitive, motor and sensory problems. The technique promises to allow researchers to create enough OPCs for widespread therapeutic use. The system also has the advantage of creating OPCs that come from a patient's own cells and are therefore genetically identical, thus avoiding the problem of immune rejection, which is a major complication in transplantation medicine.

Physician-Scientists Move Closer to Stem Cell Therapy for Deadly Skin Disease

A team of scientists at the institute is moving forward with plans to combine stem cell science and gene engineering to cure a devastating genetic skin condition called epidermolysis bullosa, or EB. People with a version of the condition called dominant dystrophic EB suffer severe blistering and sloughing of the skin that is usually lethal by young adulthood. The team will create patient-specific iPS cells from the skin cells of EB patients, engineering in the gene for the missing protein, and direct the iPS cells to grow into sheets of normal skin cells. These new skin cells will then be transplanted onto EB patients, where they will grow and regenerate like normal skin. Using iPS cells has the advantage that the new skin will come from the patients' own cells, reducing the rejection problem common to most transplantation.

Members of the Marius Wernig laboratory

The use of stem cells to treat this skin disease will serve as a testing ground and model system for future stem cell treatments, since any stem cells transplanted in the skin can be monitored,

and easily removed if problems arise. If Stanford researchers can create a successful model for stem cell transplantation for EB, they will more likely be successful using stem cells to treat much less accessible organs like the heart and brain.

Hiromitsu Nakauchi, distinguished stem cell scientist, joins Stanford

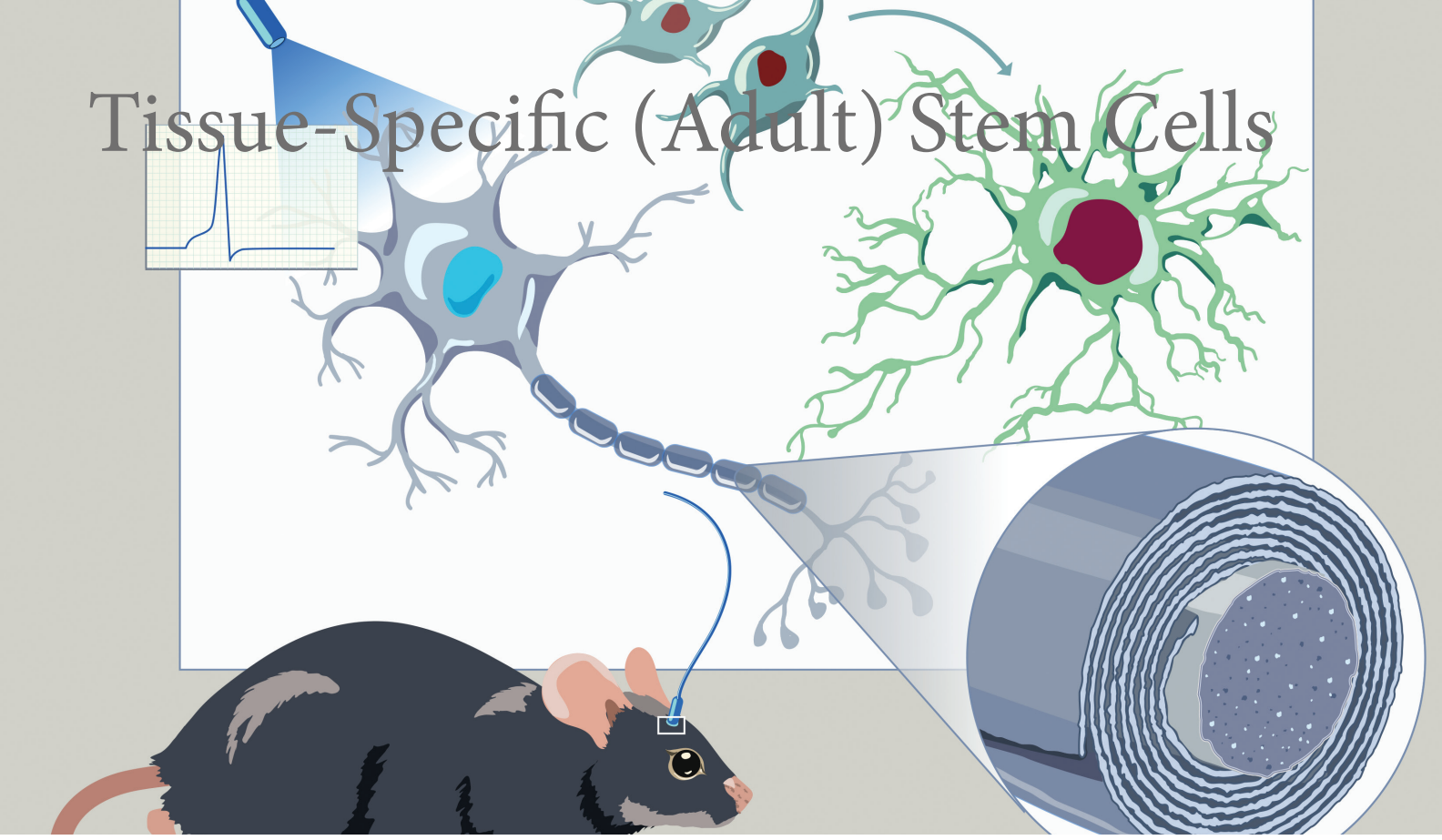
Hiromitsu Nakauchi, MD, PhD, a renowned stem cell scientist, was recently recruited to the faculty of the institute. Nakauchi, who previously directed the Center for Stem Cell Biology and Regenerative Medicine at the University of Tokyo, was the first scientist recruited to Stanford with the assistance of a $6 million research leadership award from the California Institute for Regenerative Medicine. The award is designed to help bring stem cell researchers from outside California to the state and to allow them to pursue high-risk, high-reward research.
The recruitment marked a return to Stanford for Nakauchi. After earning a medical degree from Yokohama City University and a PhD in immunology from the University of Tokyo, Nakauchi studied immune-cell genes as a postdoctoral scholar in the laboratory of the late Stanford geneticist Leonard Herzenberg, PhD.
Nakauchi then returned to Japan to study blood and immune stem cells at the RIKEN Research Institute and at the University of Tsukuba. In 2002, he became professor of stem cell therapy at the Institute of Medical Science at the University of Tokyo. In 2008, he was appointed director of the newly created Center for Stem Cell Biology and Regenerative Medicine there.
Nakauchi said he is excited to be coming back to Stanford, this time as a faculty member. Although the university has grown tremendously over the intervening years, he said, "its open, friendly and innovative atmosphere does not seem to have changed."
Nakauchi notes there are differences between the way science is done in Japan and in the United States. "My challenge will be to combine and to utilize the best parts of the systems in both countries to do innovative science and create innovative scientists," he said.

Nakauchi's Quest: Using iPS cells to Solve the Organ Donor Shortage Problem

Hiro Nakauchi's research involves clarifying the mechanisms of stem cell self-renewal and creating new medical therapies involving stem cells. One project major explores the possibility of creating individualized human organs for transplantation in large animals.
Currently, the options for patients with failing or diseased organs are limited because suitable donor organs often cannot be found. Some stem cell scientists have explored the possibility of creating new organs from stem cells in the lab, but fully functional organs are shaped by complex interactions with other organs and tissues during development.
Nakauchi has pioneered an approach that may allow stem cells from a patient to become the seeds for new, genetically matched organs that are grown in large animals. Once mature, those organs could be transplanted into the patient. Such organs could also become model systems for drug or human health research.

Hiromitsu Nakauchi, MD, PhD

Tissue-Specific (Adult) Stem Cells



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.

Stanford researchers discover precursor cell for bone, cartilage, blood and stromal cells

Researchers in the laboratory of institute scientist Michael Longaker, MD, have for the first time identified a single cell that is a common precursor to three important cell types: bone, cartilage and the stromal niche cells that support blood and immune cell growth.

Bones provide the rigid framework for our body plan, cartilage lends flexibility to the joints so we can move around, and everything is fueled and aerated by blood, which is produced in bone marrow niches. Through extensive and deliberate work, the scientists found the single kind of cell that can give rise to these three tissue types.

The researchers call this newly discovered cell the bone, cartilage, and stromal progenitor (BCSP). Understanding the BCSP will give scientists insight into how bone and cartilage repair and regenerate themselves, how the hematopoietic system can be stimulated to fight infections and cancer, and how they can make more blood to replace blood lost in accidents or surgery.

One of the key findings of this research is that the BCSPs make many types of stromal cells—the cells that support the blood and immune cells. It helps explain the mystery of how one stem cell can turn into such wildly different cell types, such as red blood cells, platelets, macrophages, and B and T cells. The interaction between stromal cells and blood cells may also lead to answers about certain diseases. The cells that support blood-forming stem cells and their immediate progeny control not only normal blood formation, but almost certainly control the early stages of pre-leukemia.

Michael Clarke, MD

Faulty stem cell regulation may contribute to cognitive deficits associated with Down syndrome

The learning and physical disabilities that affect people with Down syndrome may be due at least in part to defective stem cell regulation throughout the body, according to researchers in the laboratory of Michael Clarke, MD at the Stanford Institue for Stem Cell Biology and Regenerative Medicine. The defects in stem cell growth and self-renewal observed by the researchers can be alleviated by reducing the expression of just one gene on chromosome 21, they found.

The finding marks the first time Down syndrome has been linked to stem cells, and addresses some long-standing mysteries about the disorder. Although the gene, called Usp16, is unlikely to be the only contributor to the disease, the finding raises the possibility of an eventual therapy based on reducing its expression.

The finding raises hope that therapies can be developed to modulate the level of protein created by Usp16. There is even the possibility that such treatments could reverse some of the deficits seen in children who have been living with Down syndrome for years.

Researchers shut the door on search for small embryonic-like cells

This year, scientists at the institute made an exhaustive effort to find a theorized, very small pluripotent cell and reported they have been unable to identify such a cell in the bone marrow of mice.

Embryonic stem cells have long been believed to be the only naturally occurring pluripotent cells (cells that can become any other cell in the body). But some people object to the fact that the embryo is destroyed during their isolation. In 2006, a few researchers around the world described another possible alternative: they proposed that there was a special population of very small, pluripotent, embryonic-like cells in adult bone marrow of mice and humans. These cells, called VSEL (very small embryonic-like) cells, presumably arise through the self-renewal of embryonic stem cells during the developmental process and, as described, could provide all the benefits of embryonic stem cell research with none of the ethical controversy.

However, subsequent research from other labs has provided conflicting results as to the pluripotency — and even the existence — of VSEL cells in bone marrow. The recent research from Stanford scientists makes it very unlikely that such cells exist.

Michelle Monje, MD, PhD

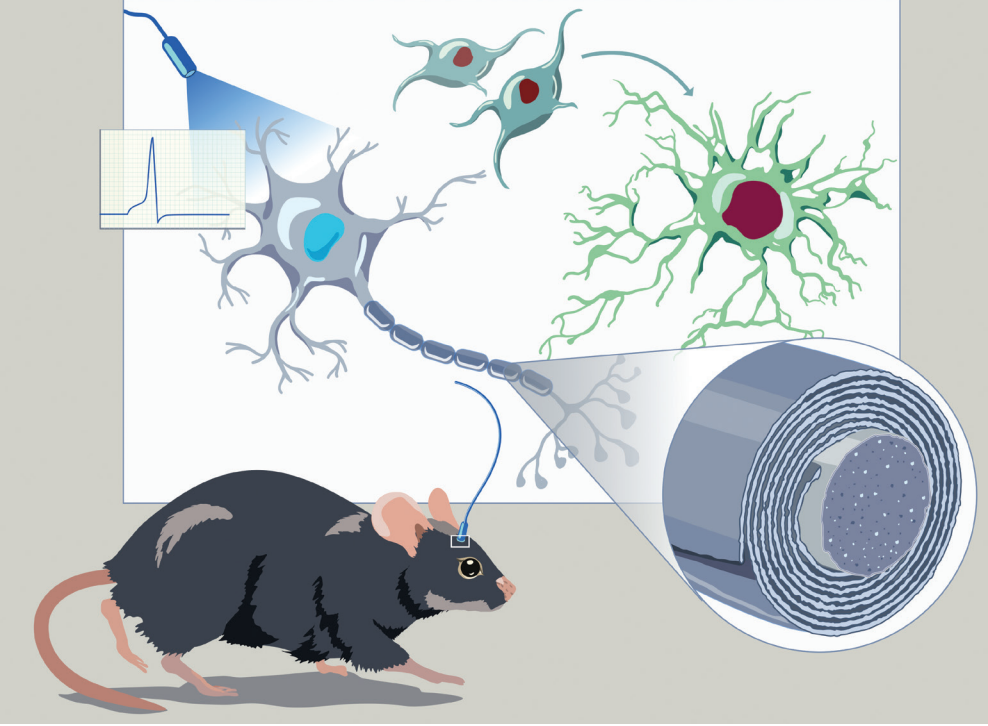
Neural activity promotes brain plasticity through myelin growth, researchers find

The brain is a wonderfully flexible and adaptive learning tool. For decades, researchers have known that this flexibility, called plasticity, comes from selective strengthening of well-used synapses — the connections between nerve cells.

Now, researchers at the Stanford University School of Medicine have demonstrated that brain plasticity also comes from another mechanism: activity-dependent changes in the cells that insulate neural fibers and make them more efficient. These cells form a specialized type of insulation called myelin.

"Myelin plasticity is a fascinating concept that may help to explain how the brain adapts in response to experience or training," said Michelle Monje, MD, PhD, a member of the institute and an assistant professor of neurology and neurological sciences. Sending neural impulses quickly down a long nerve fiber requires insulation with myelin, which is formed by a cell called an oligodendrocyte that wraps itself around a neuron. Even small changes in the structure of this insulating sheath, such as changes in its thickness, can dramatically affect the speed of neural-impulse conduction. Demyelinating disorders, such as multiple sclerosis, attack these cells and degrade nerve transmission, especially over long distances.

Myelin-insulated nerve fibers make up the "white matter" of the brain, the vast tracts that connect one information-processing area of the brain to another. "If you think of the brain's infrastructure as a city, the white matter is like the roads, highways and freeways



Nerve fibers were stimulated with light using optogenetic techniques, which were key to identifying the effects of nerve activity.

that connect one place to another," Monje said.

In the study, Monje and her colleagues showed that nerve activity prompts oligodendrocyte precursor cell proliferation and differentiation into myelin-forming oligodendrocytes. Neuronal activity also causes an increase in the thickness of the myelin sheaths within the active neural circuit, making signal transmission along the neural fiber more efficient. It's much like a system for improving traffic flow along roadways that are heavily used. As with a transportation system, improving the routes that are most productive makes the whole system more efficient.

The solution was a relatively new and radical technique called optogenetics. Scientists insert genes for a light-sensitive ion channel into a specific group of neurons. Those neurons can be made to fire when exposed to particular wavelengths of light. In the study, Monje and her colleagues used mice with light-sensitive ion channels in an area of their brains that controls movement. The scientists could then turn on and off certain movement behaviors in the mice by turning on and off the light. Because the light diffuses from a source placed at the surface of the brain down to the neurons being studied, there was no need to insert a probe directly next to the neurons, which would have created an injury.

By directly stimulating the neurons with light, the researchers were able to show it was the activation of the neurons that prompted the myelin-forming cells to respond.

Further research could reveal exactly how activity promotes oligodendrocyte-precursor-cell proliferation and maturation, as well as dynamic changes in myelin. Such a molecular understanding could help researchers develop therapeutic strategies that promote myelin repair in diseases in which myelin is degraded, such as multiple sclerosis, the leukodystrophies and spinal cord injury.

"Conversely, when growth of these cells is dysregulated, how does that contribute to disease?" Monje said. One particular area of interest for her is a childhood brain cancer called diffuse intrinsic pontine glioma. The cancer, which usually strikes children between 5 and 9 years old and is inevitably fatal, occurs when the brain myelination that normally takes place as kids become more physically coordinated goes awry, and the brain cells grow out of control.

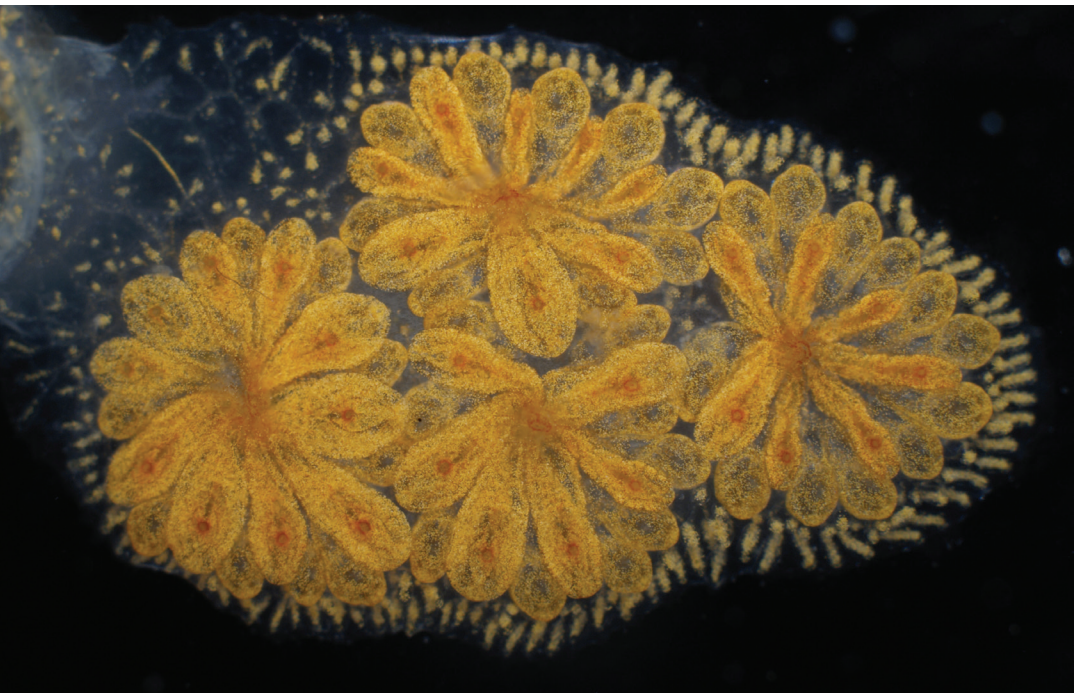
Gene determines acceptance, rejection of stem cells from others of the same marine species

To live together harmoniously in our bodies, cells need to be able to distinguish which of those among them are sanctioned residents and which are interlopers. This way, native cells can be left alone to do their jobs, and foreign cells can be attacked and removed.

The ability to identify friend from foe is made possible by the major histocompatibility genes, or MHC genes, which in humans and other vertebrates determine, for example, that a pregnancy is OK but organ transplants must be rejected (thus the need for immunosuppressants).

Now, researchers studying a marine organism called Botryllus schlosseri in the laboratory of Irv Weissman, MD, have discovered a single gene that determines whether cells are accepted as self or destroyed by immune cells as non-self. Most important, the gene determines whether circulating germ-line stem cells (which can make sperm or eggs) from one Botryllus organism can invade and implant themselves in a related Botryllus organism.

The discovery reveals a gene and its many variants (alleles) that are unique and not directly related to the human MHC genes. However, the discovery of very primitive self-recognition gene variants should enhance our understanding of the evolution of the immune system, the scientists say. Publication of the gene sequences will allow researchers to explore how MHC genes work and to look for related human genes that might be involved in self/non-self-recognition.



Botryllus schlosseri is a marine organism which is unusual in the way that related individuals live together in a colony.

Botryllus schlosseri is an unusual marine organism, an invertebrate that is evolutionarily one of the closest living relatives of vertebrates. The researchers established this relationship in another study of the organism's entire genome sequence.

The larval-stage Botryllus, which has a primitive brain and ventral neural chord (like a proto spinal cord), undergoes a metamorphosis to become an invertebrate. On a weekly basis, the invertebrate form of Botryllus reproduces by budding off new organisms. The individuals live together in a colony surrounded by a membrane or "tunic," fusing with one another other to form a shared circulatory system that moves fluid through the whole colony. However, when two or more adjacent colonies touch, a recognition event occurs. Those colonies that share one or both alleles of the compatibility gene, called Botryllus histocompatiblity factor, fuse vessels and share blood-borne cells, while those that don't share a BHF gene have an inflammatory rejection that results in the formation of a scar between the colonies.

When the colonies share a common BHF-gene variant and form a common circulatory system, stem cells from one colony will travel to the other related colony and take up residence. The transplanted stem cells from one Botryllus colony can even take over the developing gonads of the other colony, turning what was once an individual into an incubator for its relatives' germ cells, said senior research scientist Ayelet Voskoboynik, PhD, a co-lead author of the paper.

"This finding reveals a fusion-rejection system that is now understood to the point where one can reliably predict, based on BHF sequences, whether the colonies will reject or fuse with each other," said Weissman. "The fact that this system is totally unrelated to human major histocompatibility genes and the immune cells that mediate human tissue transplant rejection opens the door to a deeper understanding of the system's evolution and functions."

Institute Leadership

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.

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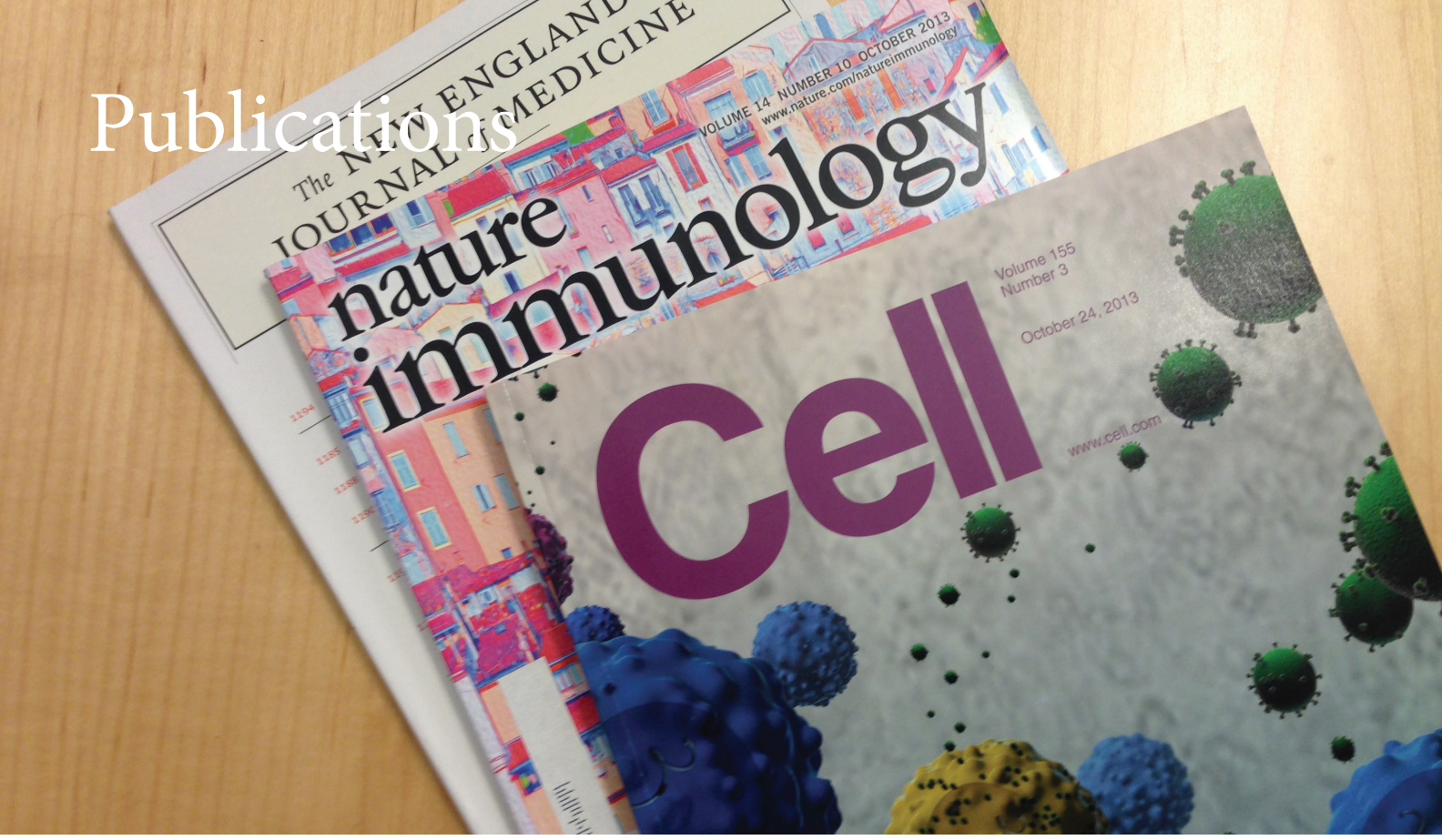

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