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Message from the Director

Dear Friends of the Institute,

I hope this last year has been good to you and your family. The ISCBRM continues to advance across many fronts of our research and educational missions. I’m excited to share that the faculty and I have undertaken a strategic planning process to develop our goals for the next five years including expanding our membership through new internal and external recruitments, developing multi-investigator research projects and grant applications, organizing into several research focus areas, building our community, and engaging broadly with the many departments, institutes, centers, and initiatives across the Stanford School of Medicine.

We hope that the ISCBRM will complement the amazing research and translational activities of our current faculty with new activities in domains including single cell studies and technology, manipulation of cell fate directly in living organisms, and modulation of immunological interactions with stem cell biology. We think these are key areas to advance our research and translational goals to have broad impact for science and patients.

To ensure success in achieving our goals, I am delighted to have recruited Heather Gentner as our new Director of Finance and Administration. Heather brings a wealth of experience at Stanford, in academic research management, and leadership. We hope to share more details in the coming year. As always, we thank you for your support and look forward to your continued partnership with the ISCBRM.

Best Regards,

Ravi Majeti MD, PhD
Virginia and D.K. Ludwig Professor
Professor of Medicine, Hematology
Director, Institute for Stem Cell Biology and Regenerative Medicine
Stanford University School of Medicine

Tissue Stem Cells in Health and Disease

Stem cell science and technology has massive potential applications for maintaining healthy tissue function and treating a wide range of diseases such as cancer, Alzheimer’s and COVID. Stem cell applications also offer hope of curing diseases that are currently incurable. One of the institute’s primary goals is to translate research findings in our labs into therapies that can be used in clinics.
Researchers find success using stem cell therapy in mouse model of Alzheimer’s disease

Researchers at the institute have shown that cell transplantation can be used to treat Alzheimer’s disease in a mouse model, raising the hope that cell therapy might be a viable treatment for human Alzheimer’s patients in the future.

“This is a great proof-of-concept demonstration that we can replace defective brain cells with transplanted blood cells,” says Professor of Pathology Marius Wernig, MD, PhD. “This cell therapy approach is unique in the field because most researchers are working to find pills or injectables to treat Alzheimer’s disease.”

Despite extensive research on Alzheimer’s disease, the cause and development of the neurodegenerative disorder is not well understood. Most therapies focus on clearing the buildup of amyloid plaques found in familial Alzheimer’s disease (AD), even though there is not a clear connection between clinical signs of AD and the presence of these plaques.

There is, however, a clear association between non-familial, late onset AD and variations in microglia—brain cells that protect other brain cells against invaders and function as a cleanup crew, taking out the metabolic trash that can accumulate in the working brain.

Scientists looking at Alzheimer’s disease in humans have observed that certain genetic variations in brain cells called microglia show a strong correlation with their risk of getting AD. One of the strongest associations is between AD and a microglia associated gene called TREM2. “In fact, genetic variants of TREM2 are among the strongest genetic risk factors for Alzheimer’s disease,” Wernig says.

“The data are convincing that microglial dysfunction can cause neurodegeneration in the brain, so it makes sense that restoring defective microglial function might be a way to fight neurodegeneration in Alzheimer’s disease,” Wernig said.

Wernig and his colleagues worked with a mouse model of Alzheimer’s disease in which the mice were bred to have a defective TREM2 gene. They then transplanted blood stem and progenitor cells from healthy mice which led to a restoration of normal TREM2 activity, Wernig said.

Next, they asked if the restored TREM2 activity was enough to positively affect the pathologies that the TREM2 deficient mice exhibited. “Indeed, in the transplanted mice we saw a clear reduction in the deposits of amyloid plaques that normally afflict TREM2 deficient mice,” Wernig said. They were also able to show improvement in a number of other disease-associated signatures that indicate that restoring the function of this one gene has widespread positive effects.

Wernig and colleagues point out that they could potentially even transplant cells that had been engineered to have supercharged TREM2 activity for even greater effect. They caution, however, that the microglia derived from the transplanted cells are slightly different than the natural microglia in the brain. “These differences might in some way have their own detrimental effect on neurodegeneration,” Wernig said.

“We have to be cautious that transcription of the blood stem cells require a highly toxic preconditioning to kill off native blood stem cells. This would make the current procedure highly risky if it were eventually developed into a human therapy. However, many researchers, including some at the Institute for Stem Cell Biology and Regenerative Medicine, are developing less toxic methods of preconditioning for stem cell transplants.

Institute scientists transform cancer cells into weapons against cancer

Researchers found that when they turned cancer cells into immune cells, the transformed cells were able to teach other immune cells how to attack cancer.

Some cities fight gangs with ex-members who educate kids and starve gangs of new recruits. Stanford Medicine researchers have done something similar with cancer — altering cancer cells so that they teach the body’s immune system to fight the very cancer the cells came from.

“This approach could open up an entirely new therapeutic approach to treating cancer,” said Ravi Majeti, MD, PhD, a professor of hematology and the study’s senior author. The research was published March 1 in Cancer Discovery. The lead author is Miles Linde, PhD, a former PhD student in immunology who is now at the Fred Hutchinson Cancer Institute in Seattle.

Some of the most promising cancer treatments use the patient’s own immune system to attack the cancer, often by taking the brakes off immune responses to cancer or by teaching the immune system to recognize and attack the cancer more vigorously. T cells, part of the immune system that learns to identify and attack new pathogens such as viruses, can be trained to recognize specific cancer antigens, which are proteins that generate an immune response.

For instance, in CAR T-cell therapy, T cells are taken from a patient, programmed to recognize a specific cancer antigen, then returned to the patient. But there are many cancer antigens, and physicians sometimes need to guess which ones will be most potent.

A better approach would be to train T cells to recognize cancer via processes that more closely mimic the way things naturally occur in the body — like the way a vaccine teaches the immune system to recognize pathogens. T cells learn to recognize pathogens because special antigen presenting cells (APCs) gather pieces of the pathogen and show them to the T cells in a way that tells the T cells, “Here is what the pathogen looks like — go get it.”

Something similar in cancer would be for APCs to gather up the many antigens that characterize a cancer cell. That way, instead of T cells being programmed to attack one or a few antigens, they are trained to recognize many cancer antigens and are more likely to wage a multipronged attack on the cancer.

Now that researchers have become adept at transforming one kind of cell into another, Majeti and his colleagues had a hunch that if they turned cancer cells into a type of APC called macrophages, they would be naturally adept at teaching T cells what to attack.

“We hypothesized that maybe cancer cells reprogrammed into macrophage cells could stimulate T cells because those APCs carry all the antigens of the cancer cells they came from,” said Majeti, who is also the RZ Cao Professor, assistant director of the Insti-
Cell conversion

The study builds on prior research from the Majeti lab showing that cells taken from patients with a type of acute leukemia could be converted into non-leukemic macrophages with many of the properties of APCs.

In the current study, the researchers programmed mouse leukemia cells so that some of them could be induced to transform themselves into APCs. When they tested their cancer vaccine strategy on the mouse immune system, the mice successfully cleared the cancer.

“When we first saw the data showing clearance of the leukemia in the mice with working immune systems, we were blown away,” Majeti said. “We couldn’t believe it worked as well as it did.”

Other experiments showed that the cells created from cancer cells were indeed acting as antigen-presenting cells that sensitized T cells to the cancer.

“What’s more, we showed that the immune system remembered what these cells taught them,” Majeti said. “When we reintroduced cancer to these mice over 100 days after the initial tumor inoculation, they still had a strong immunological response that protected them.”

“We wondered, if this works with leukemias, will it also work with solid tumors?” Majeti said. The team tested the same approach using mouse fibrosarcoma, breast cancer, and bone cancer. “The transformation of cancer cells from solid tumors was not as efficient, but we still observed positive results,” Majeti said. With all three cancers, the creation of tumor-derived APCs led to significantly improved survival. Lastly, the researchers returned to the original type of acute leukemia. When the human leukemia cell-derived APCs were exposed to human T cells from the same patient, they observed all the signs that would be expected if the APCs were indeed teaching the T cells how to attack the leukemia.

“We showed that reprogrammed tumor cells could lead to a durable and systemic attack on the cancer in mice and a similar response with human patient immune cells,” Majeti said. “In the future we might be able to take out tumor cells, transform them into APCs and give them back to patients as a therapeutic cancer vaccine.”

“Ultimately, we might be able to inject RNA into patients and transform enough cells to activate the immune system against cancer without having to take cells out first,” Majeti said. “That’s science fiction at this point, but that’s the direction we are interested in going.”

Intermittent fasting spurs proliferation of liver cells in lab mice, institute researchers find

Intermittent fasting — abstaining from eating for lengthy periods of time — spurs liver cells in laboratory mice to divide rapidly, according to a study led by researchers at Stanford Medicine. The finding challenges the long-standing belief that cells in the adult liver divide rarely and, when they do, primarily to repair damage to the organ. It is also the first to show an immediate effect of diet on liver cell biology.

“One of the most defining characteristics of the adult liver has been that it is fairly stable in terms of cell turnover,” said Roeland Nusse, PhD, professor of developmental biology. “But we found the turnover of cells in the liver goes up dramatically after several periods of 24-hour fasting followed by refeeding. Interestingly, this type of diet mirrors the natural diet of wild animals and of early humans, before the development of agriculture, when there were periods with scarce or absent food.”

It’s not known what, if any, effect the increased cell replication has on the health of the animals. But the finding implies that liver biology is more dynamic and responsive to dietary changes than previously believed, and it raises the question as to how other diets might affect its biology.

Nusse, who is the Reed-Hodgson Professor in Human Biology and the Virginia and Daniel K. Ludwig Professor in Cancer Research, is the senior author of the study, which was published online Jan. 31 in eLife. Former postdoctoral scholar Abby Sarkar, PhD, is the first author of the research.

The liver’s job

The liver is one of the largest organs in the body, weighing about 3 pounds in an adult human, or roughly 2% of one’s body weight. In mice, it accounts for nearly 5% of body weight. The liver removes toxins from the blood for excretion, and it converts the food we eat into nutrients the body can absorb. “Abby Sarkar wondered if an organ like the liver that is so involved in digestion would exhibit altered patterns of cell divisions, or turnover, when an animal’s
diet changed,” Nusse said. Laboratory mice typically have unlimited access to food at all times. But for these experiments, Sarkar withheld food from the animals for 24 hours, then allowed them to feed freely for 24 hours before another fast of 24 hours. She then analyzed cell division in the animals’ livers after one week and three weeks of the intermittent fasting diet and compared it with that of animals that had been fed normally.

“We saw that the turnover of cells in the liver went up fairly dramatically shortly after refeeding began,” Nusse said. “There were many more new cells than in animals that had been fed on a standard diet. This was very exciting.”

The liver’s role in metabolism means that the ratio between the weight of the liver and that of the body must remain constant to allow the organ to function efficiently. This is the reason the liver will regenerate to its normal size if a portion of it is removed due to injury or surgery.

Sarkar found that the cell division she observed was sparked by a decrease in the ratio of liver to body weight in the study animals after a week of intermittent fasting. She also learned that most of the cell division was localized to liver cells near the central vein of the organ.

Further investigation identified two molecular pathways responsible for maintaining appropriate liver size in the fasted animals. One is a growth factor called fibroblast growth factor, or FGF, that is produced by the intestines and travels throughout the body; another, a family of proteins called Wnts, is crucial to the development and maintenance of many tissues. Wnt proteins are secreted by endothelial cells in the central vein, but, unlike FGF, they travel only a short distance. The two signals overlap on liver cells near the central vein and can inhibit cell proliferation in the liver due to fasting has health benefits. But it’s an intriguing look into how dietary changes can affect one of the largest organs in the body. They are now planning to extend their studies to include other types of diets, including ketogenic or high-fat.

“I wouldn’t recommend that people start intermittently fasting to improve their liver health,” Nusse said. “But it’s an exciting observation — it shows that the idea that the liver is a tissue that turns over slowly should be taken with a grain of salt.”

Cells in the adult liver were thought to divide rarely. But a study led by institute researchers found that intermittent fasting causes rapid cell division

FGF is. Intermittent fasting or other changes in the food supply stimulate the production of FGF, which circulates to the liver. It wakes the liver cells from resting, then Wnt proteins give those near the central vein the signal to divide.” Sarkar next tested the effect of intermittent fasting in mice that had been genetically engineered to be unable to respond to either the FGF signal or the Wnt signal. In that phase of the research, “The effect of intermittent fasting was attenuated,” Nusse said. “The cells more or less lost their ability to divide. This is a very strong indication that you need both these signaling pathways to see this effect of fasting on cell replication.”

The researchers don’t know whether the increased cell proliferation in the liver due to fasting has health benefits. But it’s an intriguing look into how dietary changes can affect one of the largest organs in the body. They are now planning to extend their studies to include other types of diets, including ketogenic or high-fat.

“I wouldn’t recommend that people start intermittently fasting to improve their liver health,” Nusse said. “But it’s an exciting observation — it shows that the idea that the liver is a tissue that turns over slowly should be taken with a grain of salt.”

Scarf tissue holds hints about pancreatic cancer outcome, patient longevity

Scarf tissue that forms around a growing pancreatic tumor called a pancreatic ductal adenocarcinoma harbors valuable clues as to how long people with these cancers are likely to live, according to a new study led by researchers at Stanford Medicine.

The architecture and organization of cells in the scar tissue can be used to categorize patients into two groups. Members of one group lived a median of nearly two years longer than members of the other group — a substantial difference for a cancer with a five-year survival rate after surgery of only 20% to 25%.

In fact, the researchers found that the patterns of a patient’s scar tissue are among the most predictive prognostic elements for this type of cancer — second only to the stage of the tumor at diagnosis. The finding suggests that cells in the scar tissue, as well as its overall structure, interact with the cancer cells to either egg on or tamp down their growth. Drugs that intercept pro-growth messages, or mimic cellular conversations that discourage growth, may lead to new avenues of therapy.

“Our study puts new therapeutic approaches on the table,” said professor of surgery Michael Longaker, MD. “Should we be treating not just the tumor but also the scar tissue? I would say yes. Both obviously play a role in patient outcome.”

Longaker, the Deane P. and Louise Mitchell Professor in the School of Medicine, is the senior author of the study. Post-doctoral scholar Jason Guo, PhD, and former graduate student Shamik Mascharak, MD, PhD, are the lead authors of the research.

Deaths from pancreatic ductal adenocarcinoma, the most common type of pancreatic cancer, are rising, and it is projected to be the second leading cause of cancer deaths in the next 10 years. Because of the disease’s metastasizes, or invades other parts of the body, early and quickly, it often recurs within two years of initial treatment.

Pancreatic ductal adenocarcinoma sparks a particularly strong response by cells called fibroblasts found in the connective tissue surrounding the pancreas. The fibroblasts secrete collagen and other components of what’s known as the extracellular matrix to bind the tumor in a web of cancer-associated scar tissue called desmoplasia. Earlier research has hinted that this scar tissue affects patient prognosis, but the analyses were confined primarily to simple quantitative measurements.

“Previous studies have focused on the cancer cells themselves, or how much fibrosis, or scarring, surrounds the tumor,” Guo said. “But our findings reveal that maybe the critical information comes not from the quantity or mass of the scar tissue, but from its internal components and organization.”

Guo and his colleagues studied hundreds of samples of pancreatic ductal adenocarcinoma tissue collected during surgery to remove the cancerous portion of the pancreas — for the condition. They used a computer algorithm to identify and analyze nearly 300 distinct attributes of the desmoplasia, including the length, width, alignment and...
Longaker, Guo and their colleagues hope that new information about the contributions of the desmoplasia to pancreatic cancer growth will not just open doors for new therapies but that it will also be used to guide clinical decisions.

"In the future, I envision that a patient gets a biopsy before treatment has started, and doctors will look not just at the cancer but also at the patterns and types of cells in the desmoplasia," Longaker said. "This could also help doctors decide which patients are likely to need more aggressive therapy early in the course of their disease, and who could be spared invasive or harsh chemotherapy or radiation. I hope we can develop a chemotherapeutic approach that doesn't just focus on the cancer but that also impacts fibroblasts and their role in promoting tumor growth."

Researchers from the University of Virginia School of Medicine contributed to the work.

Runaway immune reactions cause long COVID breathing problems

Institute researchers have found a mechanism behind one of the most common symptoms of long COVID -- shortness of breath. Post COVID-19 breathing problems are caused by a condition known as lung fibrosis, when damaged lungs form scar tissue, which makes it difficult for lungs to expand and contract. Long COVID cases can be severely debilitating and resistant to treatment, said Gerlinde Wernig, MD, PhD, assistant professor of pathology, who led the study. What's worse, lung function can continue to decline, even without a new COVID-19 infection. The team's new research pinpoints what's happening in the lungs to cause fibrosic overactivity of genes that regulate inflammation and immune responses. The finding, which was published in the Proceedings of the National Academy of Sciences in February, offers hope that, one day, targeted drugs could intervene to quell the genes behind the damage, something they've already testing out in mouse studies, Wernig said.

"This was an extension of our work with chronic pulmonary fibrosis," said Wernig. Previously, Wernig and her colleagues conducted research showing that the dysregulation of particular immune processes caused fibrosis in the lungs. Wernig wondered if something similar was happening in the lungs of people with long COVID.

The team started by looking at lung tissue samples from five COVID-19 patients who had had symptoms of the disease -- such as shortness of breath -- for one or more months. The lungs of people who had symptoms after infection with SARS-CoV-2 (the virus that causes COVID-19) looked like the lungs of people with end-stage pulmonary fibrosis, said Wernig.

By analyzing single cells from the patients' tissue samples, the scientists also saw similarities in the pattern of RNA production -- which can hint a cell's overall function -- between samples of tissue from long COVID patients and samples from patients with pulmonary fibrosis.

"We saw this same pattern across all human COVID lung samples," Wernig said. As with other lung infections, the initial COVID-19 infection in the lungs kicked off an inflammatory process. In the case of long-COVID patients, however, the immune dysfunction keeps going long after the virus is gone -- similar to what happens in chronic pulmonary fibrosis.

In her previous research, Wernig showed that pulmonary fibrosis was characterized by a spike in the production of an inflammatory marker called interleukin-6 in the lungs, which is associated with chronic inflammation and scar formation. Furthermore, in pulmonary fibrosis, scar-forming cells called fibroblasts increase production of a protein called CD47, which stops the immune system from keeping fibroblasts under control, meaning scar tissue forms unchecked. The researchers also saw increases in a protein called pJUN, which is a key promoter of scar formation.

To test whether lung fibrosis could be firmly connected to COVID-19 infections, they looked at lung fibrosis in mice infected with a SARS-CoV-2-like virus and found significant increases in fibrosis and immune dysfunction. "Innate immune cells go crazy after that infection," Wernig said, referring to the part of the immune system that forms the first line of defense against pathogens.

In a mouse model engineered to more closely rewire human biology, researchers showed that, when the mice contracted SARS-CoV-2, scarring in the lung tissues shot up, as did levels of interleukin-6, CD47 and pJUN. There was also a bright side to these experiments. "When we did the same experiments but blocked CD47 and II-6, we saw very little fibrosis," Wernig said. "This hints at possible treatments for long COVID involving drugs that carry out targeted immune blockades."
Blood condition called CHIP linked to protection against Alzheimer’s

Stanford Medicine researchers have found that a common blood condition associated with several diseases may have a protective effect against Alzheimer’s disease. In the condition, clonal hematopoiesis of indeterminate potential, or CHIP, certain blood stem cells acquire mutations that strengthen their ability to survive and multiply. As a result, the mutant cells dominate, and just a few cells can give rise to much or even all of the body’s blood and immune cells. In most cases of CHIP, a dominant blood stem cell gives rise to between 4% and 30% of blood and immune cells.

Studies by Stanford Medicine assistant professor of pathology Siddhartha Jaiswal, MD, PhD, and others have shown that people with CHIP are at much higher risk of developing various diseases. By analyzing medical databases and stored blood samples, Siddhartha and his colleagues have shown that people with CHIP are about twice as likely to develop coronary heart disease, twice as likely to develop chronic liver disease and 10 times as likely to develop blood cancers such as myeloid leukemias. Researchers don’t yet fully understand why CHIP is linked to diseases other than blood cancer, though some studies have suggested that CHIP mutations cause increased activation of the immune system.

Jaiswal and his colleagues investigated an association between CHIP and Alzheimer’s disease, expecting to see either no association or a positive association with Alzheimer’s disease. By analyzing medical databases and stored blood samples, Jaiswal and his colleagues have shown that people with CHIP are about twice as likely to develop Alzheimer’s disease. However, the researchers found that between 30% and 50% of Alzheimer’s cases were found to have a 30% to 50% lower risk of developing Alzheimer’s disease, “Jaiswal said. People with CHIP were found to have a 30% to 50% lower risk of developing the neurodegenerative disorder, compared with those who did not have the CHIP mutation, he said.

“The degree of protection from Alzheimer’s disease seen in CHIP carriers is similar to carrying an APOE ε2 allele,” said Jaiswal, referring to a genetic variant that’s known to decrease the risk of Alzheimer’s.

Siddhartha Jaiswal, PhD

The team saw the negative association with Alzheimer’s and CHIP even when they accounted for other risk factors. “We thought there might be some kind of survivor bias — that people with CHIP were more likely to die before developing Alzheimer’s disease — but the decrease in risk still held after adjusting for that,” Jaiswal said. They also analyzed the association in another way, to see if people who had Alzheimer’s disease were less likely to have CHIP. The researchers confirmed that they were. A paper published on June 15 in Nature Medicine detailed the findings.

Digging deeper

Of course, an association doesn’t mean that there is a cause-and-effect relationship. So, Jaiswal and his colleagues conducted different forms of genetic analyses, finding evidence that CHIP could causally inhibit the development of Alzheimer’s. The connection between CHIP and Alzheimer’s implied a somewhat unexpected link between brain cells and the cells that give rise to blood and the immune system, Jaiswal said.

“We were surprised to find that CHIP mutations seem to exist in microglia cells. The investigators found that between 30% and 90% of the microglia in brain samples of those with CHIP harbored the CHIP mutations. The proportion of mutant microglia in any individual brain tended to match the proportion of mutant blood cells in the rest of the body.

“This suggests that cells are migrating from the blood into the brain,” said Jaiswal, adding that the finding is in contradiction to the accepted dogma. “It’s a remarkable finding.”

How this affects the development of Alzheimer’s disease is not yet clear, but researchers know that microglia help fight microbial invaders and clean up waste products in the brain. “One hypothesis is that the mutations that promote a growth advantage in blood stem cells also promote microglial expansion and activity, boosting microglia’s ability to fight the conditions that lead to brain disease,” Jaiswal said.

The scientists also saw that, in the brain samples of people with CHIP, levels of neurofilibrillary tangles and amyloid plaques, both associated with Alzheimer’s disease and thought to be causative, were lower.

Jaiswal and his colleagues are planning follow-up studies to learn more about how the mutated microglia might be protecting against Alzheimer’s disease. Jaiswal plans to work with professor of pathology Marius Wernig, MD, PhD, to transform CHIP blood stem cells into microglia so they can understand how these cells behave differently than normal microglia.

Although there’s much work to be done, the researchers hope that if they are able to understand these mechanisms, it could help guide the development of new therapeutics that could one day protect against Alzheimer’s disease, they said.
Why does CHIP lead to cardiovascular disease?  
The answers are becoming clearer

Some people, as they age, get a condition in which mutant blood stem cells gain a competitive advantage over other blood stem cells and begin to take over. People with this condition, called CHIP (clonal hematopoiesis of indeterminate potential), will harbor a clone of blood and immune cells derived from a single mutant stem cell. Previous research has shown that people with CHIP may seem perfectly healthy, and yet are at higher risk for atherosclerosis, blood cancers, and other diseases.

Institute researchers have now shown why people with CHIP may be at higher risk for some cardiovascular diseases. Assistant Professor of Pathology Siddhartha Jaiswal, MD, PhD and his colleagues have discovered that the two most common mutations in CHIP, in the genes TET2 and DNMT3A, can both induce similar inflammatory programs in mice.

Inflammation has long been associated with the atherosclerosis disease process, providing an explanation for a likely mechanism connecting mutations in these two genes and cardiovascular disease. “This was surprising, because these two genes have opposite effects biochemically,” Jaiswal said. “DNMT3A encodes an enzyme that promotes the methylation of methylcytosine, while TET2 encodes an enzyme that initiates the demethylation of methylcytosine.”

The research was published the journal Nature Cardiovascular Research. Jaiswal is senior author. Philipp J. Rauch, MD, an instructor in Medicine at Harvard Medical School, and Stanford medical student Jayakrishnan Gopakumar are first authors. The researchers tested a few possible ways that the loss of a functional DNMT3 might promote atherosclerosis. They had previously shown that stem cells with TET2 mutations gave rise to macrophages that promoted inflammation when exposed to high levels of LDL cholesterol (the “bad” cholesterol). In the end, they were able to show that macrophages derived from blood stem cells with mutant DNMT3A also promoted inflammatory processes.

“So even though these two genes have opposite effects on a basic biochemical level, the effects of the loss of function in either gene converge at the cellular level to produce a common, pro-inflammatory effect on cardiovascular tissues,” Rauch said.

Such pro-inflammatory effects might be part of the reason CHIP is associated with other diseases, the researchers note. Patients with heart failure who have mutations in TET2 or DNMT3A face a far worse prognosis than those who don’t. CHIP associated with DNMT3A mutations also raises the risk for osteoporosis. The researchers hope that by understanding some of the underlying mechanisms by which CHIP acts to raise disease risk, they might be able to come up with interventions to reduce those risks.

Pluripotent Stem Cells and Development

Much of the future of stem cell science and regenerative medicine depends on understanding exactly how stem cells differentiate and become more specialized cells. Institute researchers strive to understand how this happens in the natural world, and how to precisely replicate and control that process in the lab.
Researchers discover how to purify human neural stem and progenitor cells and map their further development in the brain

How can you study king salmon if you can’t tell them apart from any other fish? How can you study a particular kind of cell if you can’t distinguish it out from other cells? Scientists are praising recent research by Irv Weissman and his colleagues at the institute as a “tour de force” that gives researchers the ability to identify and trace the development of all important neural stem and progenitor cells that give rise to the human brain. The technique promises to open a door to fully understanding human brain development, and may offer new avenues for studying brain disorders.

The research, published in the journal Cell, has already resulted in the characterization of a functionally distinct cell type that was previously unknown. Irv Weissman, MD, is the senior author on the paper. MD/PhD student Daniel Liu is first author on the paper.

“Being able to separate cell types is central to biology,” Liu said. “In the mouse, we can use techniques like genetic lineage tracing to map cell development, but this requires genetic modification of cells in a growing brain, and of course in humans we can’t do that.”

“While most human neural cell types were known, there weren’t good ways of purifying those cells,” Liu said. “Without such purification methods, we will always be studying mixtures of different cell types.”

The researchers started with mid-gestational brain cells and looked for the presence or absence of a number of cell surface markers. They also analyzed the cells’ RNA activity. The investigators then took these characterized cells, transplanted them into mouse brain, and watched how they developed. By matching surface markers and RNA activity with developmental outcomes of the various cells, they were able to tell which markers were truly important in identifying various neural stem and progenitor cells, as well as map their respective developmental lineages.

“This method is powerful because we were able to identify purification schemes for all cell types in one go,” Liu said. “For every single cell type, we were able to show their lineage hierarchy as well as their transplant potential in a systematic way.”

One particular surprise that came out of the research concerned neural progenitor cells with high levels of the protein Thy1. Previously, such cells were thought to develop into neurons, but Weissman and colleagues found a subset of these cells that would develop into oligodendrocytes but not into neurons. The work is proof-in-principle that this method could ultimately be applied to create a complete scheme for the development of all brain cells from the very first neural stem cells to the most mature and differentiated neural cells. Such a well-defined developmental tree has been mapped out over decades for human blood and immune cells, and has proven immensely valuable for studying blood and immune disorders. A well-defined map of human brain cell development would also be hugely beneficial, the researchers say.

“There are several surprises that come from this study” said Weissman. “First, we could study the properties of these cells by transplantation into newborn immune deficient mouse brain lateral ventricles; the human stem cells migrated to the mouse ‘home’ for brain stem cells, then accurately produced all brain lineages by site appropriate events.” This implies that despite over 85 million years of evolution between mice and humans, the signals for neurodevelopment in the brain were conserved, Weissman said.

“Now the transition to postnatal and adult neurogenesis by stem cells needs to be worked out so that we and others can begin to trace their activities in the human adult brain to find out how such cells change in human brain diseases,” Weissman said. This study presents a method of achieving that well-defined map of human brain development, but there is still a lot of work to be done, the researchers say. “We have identified several more candidate markers that may further resolve heterogeneity in the hierarchy of human neural development,” Liu said. “That is something that will be the focus of future studies.”

Irv Weissman, MD

Liu says. “Being able to characterize and isolate all the various kinds of cells in the developing human brain will be a huge boon for studying brain function and disfunction, as well as help us develop clinically feasible brain stem cell transplants.”

Other Stanford scientists involved in the research were Joy He, Rahul Sinha, Anna Eastman, Angus Toland, Maurizio Morri, Norma Neff, Hannes Vogel and Nobuku Uchida.
In mathematics, physics, and engineering, it's common to take a difficult, complex problem in three dimensions and simplify it by modelling it in two dimensions. Institute researchers have done something similar in order to study stem cell development and differentiation by creating a two-dimensional, monolayer model of cell development to precisely study what is normally a hard-to-study, three-dimensional process.

“Our system has a lot of advantages,” said institute member and associate professor of obstetrics and gynecology Vittorio Sebastiano, PhD. “We are able to answer a lot of longstanding questions about human cell development.”

A common way to study cell development and differentiation is to study embryoid bodies: a cluster of pluripotent cells that specialize, or differentiate, as the cells grow and divide. Researchers can study the direct interactions between cells in the embryoid body as it grows, but they have trouble studying how the cells are affected by molecular signals that diffuse through the embryoid body, Sebastiano said.

“There are molecular signals that diffuse out from individual cells and it’s hard to know other cells in the embryoid body experience the concentration and timing of those signals,” Sebastiano said. “The way cells react to various local concentrations of signal can be very different.”

Sebastiano and his colleagues therefore went about creating an embryoid body in two dimensions, laying the cells out flat on media so that they knew precisely the concentrations and timing of various molecular signals that each cell was exposed to.

“All the cells growing on the monolayer are homogenously exposed to whatever is in the culture media (e.g., signaling factors) and we can systematically interrogate their impact on cell differentiation and development,” Sebastiano said. “The system is a boon for discovering important new cell signaling pathways, Sebastiano says. “With a three-dimensional embryoid body, you have to already know what pathways are important,” he said. “With the monolayer approach, you can guess what signals you think will be important and then test that hypothesis.”

Sebastiano teamed up with assistant professor of developmental biology Kyle Loh, PhD and Siebel Investigator Lay Teng Ang, PhD to apply to system to a specific scientific problem. Primordial germ cells (PGCs) exist early in embryonic development and are later transformed into eggs and sperm. Being able to generate PGCs from human pluripotent stem cells would help our understanding of human development and might provide future treatments for infertility.

But scientists have been stuck trying to understand how to generate PGCs because the 3-dimensional environment in which they develop is complex. Sebastiano, Loh and Ang used the simplified monolayer approach to study the exact steps that were required to transition cells from pluripotent stem cells to PGCs.

“We discovered that at a specific time in the development of the early embryo, the WNT signal needs to be active for 12 hours and then inactivated in order for PGCs to develop,” Loh said. If the WNT signal stays active for more than 12 hours, the cells go on to form the primitive streak.

Scientists also knew that embryonic stem cells and PGCs had a very similar profile of pluripotency gene expression but were uncertain if, in the process of becoming PGCs, those pluripotency genes needed to be turned off and then turned back on. “By studying the process using the monolayer system, we now know that these gene stay on and don’t shut down temporarily,” Loh and Sebastiano said.

Knowing exactly what genes are active and when they are during the developmental process will be important for regenerative medicine, Loh said. “If you want to grow organs, you need to have a precise protocol for reproducing these conditions in the lab.”

Ultimately, Sebastiano says, the work is a first step that could lead to a new understanding of how to generate youthful patient-specific ovarian tissues, which could impact women’s health and longevity, a critical goal and focus of the Sebastiano Lab.

The work was published in the journal Nature Communications.
Aging and disease are accompanied by the degeneration or destruction of various organs or tissues. The dream of regenerative medicine is to use our understanding of stem cell science to grow new cell therapies in the lab or to help the body regenerate those organs and tissues.

Growing new blood vessels when arteries are blocked

Institute researchers have discovered that certain purified stem cell components of normal body fat, when combined in the right proportions and transplanted into the body, will grow into new blood vessels. The researchers showed that when the technique was used in mice it restored blood flow to areas where arteries were blocked. The discovery may lead to effective new therapies that use people’s own fat to treat heart attacks and promote organ transplantation.

“Vascular disease is still a major cause of illness and death throughout the world, and currently we can only restore blood flow to existing arteries,” say institute member Charles Chan, PhD. “Our work shows promise that we might help the body generate large blood vessels, bypassing blocked or diseased arteries.” Chan, an assistant professor of Surgery, Patricia Nguyen, MD, an associate professor of Medicine, and Michael Longaker, MD, the Deane P. and Louise Mitchel Professor in the Stanford School of Medicine, are co-senior authors on the paper, which was published in the Journal of Arteriosclerosis, Thrombosis and Vascular Biology (ATVB). Institute member Irving Weissman, MD, was also involved in the research. Postdoctoral fellow Liming Zhao, MD, former Stanford PhD & MD student, Andrew Lee, and former Stanford bioinformatician, Koki Sasagawa, are co-first authors on the paper.

Scientists have known that the body can create small “collateral” arteries or capillaries in response to ischemia (when the supply of blood and oxygen to tissue is cut off). However, the blood vessels that grow are too small and sparse to supply an ischemic organ. As a result, researchers have been unsuccessfully trying to identify the cells that give rise to these collateral arteries, in hopes of creating a more robust arterial growth. The collateral vessels seem to arise from so-called “mesenchymal” stem cells (MSC), which include a mix of different kinds of stem and progenitor cells for bone, fat, blood vessels and various other tissues.

The researchers used an array of advanced analytical techniques to narrow down exactly which cells in the mixed MSC population were actually responsible for growing the new arteries. They focused in on two populations that they call VSPC1 and VSPC2, but were confounded to find that neither of these pure populations gave rise to functional vessels. VSPC1 cells, when transplanted into animals, gave rise to stunted, incomplete blood vessels. VSPC2 cells gave rise to stunted vessels and fat. However, when the two populations were transplanted into mice together in a particular ratio, functional new blood vessels
We found these two distinct cell populations have to be transplanted together to work because one kind of cell serves as the developmental niche that is required for the other cell to become a functional blood vessel,” Chan said. “Vessels start forming as soon as you transplant them.

The discovery is clinically important because the treatment for a heart attack or other ischemic event might be found in the patient’s own fat, Chan says. “If someone has a heart attack, you first want to deal with the blockages, but then you want to encourage new artery growth,” Chan said. “In principle, doctors could potentially use liposuction to collect a patient’s fat, separate out these two cell populations, and transplant them back into heart tissue that has been deprived of oxygen,” Chan said.

“Fat is a readily available, abundant and renewable resource in America,” Longaker said. “It is promising to be able to use it to induce new blood vessels.”

The technique could also be used for tissue transplants, Chan said. Currently, doctors performing tissue or organ transplants surgically connect only the major vessels, meaning that the tissue is not getting as much blood as it was before transplantation. “Surgeons could apply these two cell populations in a gel to the transplant area, and those cells would do the job of connecting the small vessels,” Chan said.

In addition, there is the possibility of using banked cells, collected from the fat of anyone who cared to donate. “Because these cells wouldn’t be immunologically matched to the patient, you would have to use anti-rejection drugs at first, but then you would gradually wean patients off the drugs as they regenerated their own vessels,” Chan said. “It’s like if a bridge is knocked out, you put up a pontoon bridge that you put up temporarily to keep supplies moving until you are able to repair the permanent bridge.”

Institute researcher discovers “Holy Grail” of human blood stem cell expansion in culture

Institute researcher Hiro Nakauchi, MD, PhD and his colleagues have found what has been called the “holy grail” of blood stem cell research: a way to expand the number of human blood stem cells in the lab. The discovery opens the door to new research and new therapies for diseases that are currently untreatable.

Their work is published in the journal Nature. Nakauchi shares co-authorship with Satoshi Yamazaki, PhD, an associate professor of stem cell biology at the University of Tokyo. Former Stanford postdoctoral scholar Adam Wilkinson, PhD, is one of the lead authors.

Blood stem cells (called hematopoietic stem cells or HSC) give rise to all the various blood and immune cells in the body. But HSCs are incredibly rare, and hard to isolate in large numbers. Only about 1 out of 30,000 cells in the bone marrow is a blood stem cell. This makes it difficult to obtain sufficient number of cells to do research.

Bone marrow transplantation, in which HSCs and other blood products are transplanted from one patient to another, is a well-established treatment for advanced leukemia, but opportunities to treat these cancers, as well as many other disorders, are limited by the difficulty of isolating HSCs in large volumes. Historically, HSCs can only be isolated from living organisms. Once they are out of the body, researchers have not been able to get HSCs to multiply in culture to create more HSCs.

“Clinically, the rarity of HSCs and the difficulty of isolating many of them has been an issue for over 50 years,” Nakauchi said.

Nakauchi is well aware of this issue, having been personally involved in trying to expand samples of HSCs ever since he first isolated purified mouse HSCs in the 1980s. “I thought it would be very easy to expand HSCs,” Nakauchi says. “I tried many different ways of going about it, but it never worked.”

Nakauchi and his colleagues had a breakthrough in recent years when they discovered how to expand mouse HSCs in culture, a result that they published in 2019. “Over the years I tried adding many different cytokines—molecules that prompt various cell activities—but none of them worked.”

The trick turned out to be not adding things to the culture medium, but taking things away. “The difficulty was that even very slight impurities in the culture medium, even very small amounts of inflammatory cytokines in the culture medium, would push the stem cells to differentiate into other kinds of cells,” Nakauchi said. As they had when culturing mouse HSCs, the researchers decided not to use common culture media that may be contaminated with various compounds. Instead, they used polyvinyl alcohol, a synthetic chemical that can be obtained...
in pure, uncontaminated form. But the protocol that the researchers had successfully used to expand mouse HSCs didn’t work well with human blood stem cells. To understand why, they analyzed the molecular pathways connected to the signal that prompts the stem cells to divide. They found that a certain molecular mechanism called PI3K phosphorylation was not as active in human cells as in mouse cells. Artificially boosting the activity of that pathway turned out to be the key to getting better replication of the human HSCs. Now that Nakauchi and his colleagues have found out how to grow a few human blood stem cells into many, there are new possibilities for medical therapies. Currently, people with acute leukemia can only undergo stem cell transplantation if they can find a donor who has a matching immunological profile. While Caucasian patients have an 80 percent chance of finding a match, for instance. Researchers have discovered, however, that if very large quantities of HSC are transplanted, they can take up residence in the patient’s body without the need for removing the patient’s own HSCs first. Institute researcher Matthew Porteus, MD, PhD, for instance, is interested in potentially making use of this effect to more safely transplant a blood stem cell that has been genetically modified to provide a cure for young patients with sickle cell disease. The ability to create large numbers of HSC in the lab should also be a boon for basic researchers, who will now be able to obtain the materials they need for larger, more in depth studies of blood stem function. With such wide applicability in medicine, the interest in this research has been strong. “We are getting inquiries from around the world about our results,” Nakauchi said.

Institute researchers identify three key roadblocks to stem cell therapies

As the stem cell sciences progresses rapidly, we are drawing ever closer to a world in which once incurable diseases and conditions will find treatments. But a recent review by researchers at the Institute for Stem Cell Biology and Regenerative Medicine, New York University and Harvard have identified three key roadblocks to developing discoveries into therapies: fibrosis, immune activity, and cell over-proliferation. “What was once considered the future of medicine is now becoming a reality,” said Michael Longaker, MD. “But to get to that new reality we have to be able to overcome these significant hurdles.” Longaker and his colleagues observe that nearly every human malady, be it injury, chronic disease, or degenerative disease, damages tissues in the body. The body has the capacity to heal itself, to regenerate the tissues that have been damaged, but often inflammation and fibrosis (the development of scar tissue) interferes with that regenerative process. In fact, 45% of all deaths can be traced to regenerative failures caused by inflammation and fibrosis. “I was shocked by that statistic,” Longaker said. “Following heart attack, inflammatory bowel disease, liver disease, you name it—most organs in the human body fall short of complete repair after injury.” Longaker began his career decades ago studying how scarring did not occur in the fetus, and has since continued to study why scar tissues develop or do not. “Scars are a kind of spot-weld in the skin—a quick repair that lets the person continue to survive and procreate, even though the tissue might not function quite as well as before.” But in many cases, reduction in function caused by scar tissue can lead to major problems over time. The stiffening of heart tissue caused by scarring after a heart attack make the heart muscles work harder to pump the same amount of blood, setting off a reinforcing cycle that can eventually lead to heart failure. By studying the underlying biology of scar formation, however, Longaker and his colleagues have discovered how to interfere with the signals that put cells on a path to become fibroblasts (scar tissues). With that pathway blocked, normal skin will regenerate where a scar would otherwise form. “Regeneration turns out to be the default pathway if you block other options, like fibrosis,” Longaker said. Inflammation brings its own challenges, the re-
searchers found. Inflammation is a complex response to injury by the immune system. Inflammation is largely a beneficial process that is needed to fight off invading organisms. May of the inflammatory signals are also necessary to start and maintain the regenerative process.

But inflammation can also promote fibrosis on its own, the researchers said. “Precisely targeting inflammation may ameliorate fibrosis and unlock latent regenerative capacity,” Longaker said.

The immune system is also a roadblock to promise that stem cell transplants might help injured tissues repair themselves. Unless the implanted stem cells come from the patient’s own body, the immune system is designed to recognize them as foreign invaders and attack. Currently, this attack is controlled by strong immunosuppressive medications, but these therapies have their own problems.

“The good news is that many scientists, including some in the institute such as Agnieszka Czechowicz, are currently studying ways to carefully recreate the immune system so that it doesn’t attack transplanted tissues and cells. Lastly, there is the roadblock of cell over-proliferation. “When you transplant stem cells, there is always the worry that those cells may proliferate more than you want and in a disorganized fashion,” Longaker said. Such uncontrolled growth can result in a non-cancerous mass of tissue that can interfere with bodily functions. If that were to happen to neural stem cells transplanted into the spinal cord, for instance, the resulting teratoma could squeeze the spinal column and cause paralysis.

“We can think of stem cells as seeds that we plant in the “soil” of the body,” Longaker said. “We need to think not only about the nature of the cell we are implanting, but also about the environment that the cell is going into, the ‘soil’ that will support and nurture that seed and help it grow.”

Stem cells often operate in a complex “niche,” a cradle of non-stem cells that provide key signals and support. “If you put stem cells in a hostile “soil,” you don’t get what you want. Understanding the supportive environment and the key signals that each kind of stem cell needs will be essential to overcoming this roadblock, the researchers say.

“The more we understand the better,” Longaker said. “I’m optimistic because we are now understanding these roadblocks and have potential strategies to address all of them.”

“Further understanding will require an interdisciplinary effort that brings together biologists, biomedical engineers and clinicians,” Longaker said. “What we can see in the distance is a transformed medical landscape that is able to seamlessly rejuvenate organs, ultimately extending human lifespan and health span.”

“The advancement of science and medicine depends on the development of creative new tools for investigation. Institute researchers are leaders in the development of biostatistical tools which give unprecedented insights into stem cell activity in health and disease.
Researchers invent a tool to create high-resolution maps of gene activity, opening a path to improved diagnostics and therapies

Most people aren't exactly the same everywhere they go. People act in ways that are appropriate for their environment, for the people they interact with. At work they have certain sorts of conversations, while at home, they talk about other things. On vacation, they may ride a zipline or lie on the beach, activities they do neither at home nor at work.

Cells in the human body are much the same. How a cell behaves, the proteins it produces, the signals it sends out or receives, are highly dependent on the kind of environment that cell finds itself in. Which makes all the difference for understanding biology and treating disease.

"Cells don't exist in isolation," said Aaron Newman, PhD, an Assistant Professor of Biomedical Data Science, a member of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, and the senior author of the study. "They exist in communities, in terms of what they do. Cells have to be understood based on their context and surroundings."

Newman and his colleagues have now developed a new method for profiling activity of single cells while also identifying exactly where those cells are geographically in a sample. The method, published March 6, 2023, in the journal Nature Biotechnology, is in many ways more powerful than other methods and will provide researchers with a significant new tool for drug discovery and the development of improved diagnostics, Newman said.

Newman and his colleagues are not alone in realizing the importance of spatial information in biology. "In the last few years there have been really rapid advances in the development of spatial assays," Newman said. But each method has its own limitations. 10X Visium is a tool that allows researchers to do an analysis of all the genes being expressed by cells, but the location of each gene's activity can only be narrowed down to within a spot 55 microns wide, an area that might hold dozens of individual cells. The result resembles a crime "heat map" of a city—useful for knowing generally in which areas crimes will occur, but not much use in identifying individuals who will commit crimes.

Another method, called Vizgen MERSCOPE, very accurately pinpoints the exact location of every cell, but researchers can only look at the activity of 500 genes within each cell. Since there are over 20,000 genes that might be activate in any given cell, MERSCOPE is unable to gather information about differences in cell activity that might be very important. "It's like coming to a foreign city and trying to get to know someone using only a phrase book," Newman says. "You can gather enough basic information to get a general idea of the person, but you can't ask the questions that might reveal, for instance, that this person you are meeting was also born on a farm and shares an interest in modern agricultural technology.

What Newman set out to do was combine these features and generate accurate, high-resolution spatial information while also being able to look at the activity of all 20,000 genes in each cell. He and his team accomplished this by creating a new method called CytoSPACE, which uses mathematical techniques to combine spatial assays like Visium and MERSCOPE along with an existing technology for measuring gene activity in individual cells.

As mentioned before, cells will change their behavior depending on how near or far they are from other specific kinds of cells. Some of these differences are well documented. For instance, immune cells that are cheek by jowl with cancer cells experience "immune exhaustion" and put the brakes on their immune activities in defined ways. (This discovery, and the discovery of how to take the brakes off these exhaust-ed cells and revitalize their cancer-fighting abilities, garnered a Nobel Prize in 2018.) By measuring such changes in cell state, the researchers were able to tell how far certain cells were from certain others.

CytoSPACE starts with a low resolution map of a sample that provides information on the few dozen cells a 55 micron-wide cluster, and then adds information about how near of far some of those cells are from each other. When the researchers gave that information to a computer program that sorts through all possible configurations, the correct configuration popped out. "It's like puzzling out a map of a foreign country if you only know the distances between the major cities," Newman says. "Once you get those pieces put in place, the remaining pieces can only fit in certain ways."

Being able to piece together the exact organization of cells in a sample, and being able to look at the activity level of all the genes in each cell, will open avenues to basic biological discoveries and possible new therapies for disease, Newman said. "For instance, if we didn't know anything about cell exhaustion and how to reverse that to treat cancer, that information would pop out of this sort of high-resolution, spatial analysis of cancer and immune cells," he said. "I'm sure there are cell behavioral changes, of which we know nothing about now, just waiting to be discovered once investigators start creating these information-rich, high-resolution maps."


Siddhartha Jaiswal


Natalia Gomez-Ospina


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Birth Weight Is Associated With Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Outcomes in Adulthood.

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Building human artery and vein endothelial cells from pluripotent stem cells, and enduring mysteries surrounding arteriovenous development.


Review.


A Review of Radiation-Induced Vascular Injury and Clinical Impact.


Allele-specific expression reveals genetic drivers of tissue regeneration in mice. Michael Longaker

A Review of Radiation-Induced Vascular Injury and Clinical Impact.


Remote neuronal activity drives glioma progression through SEMA4A.


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