

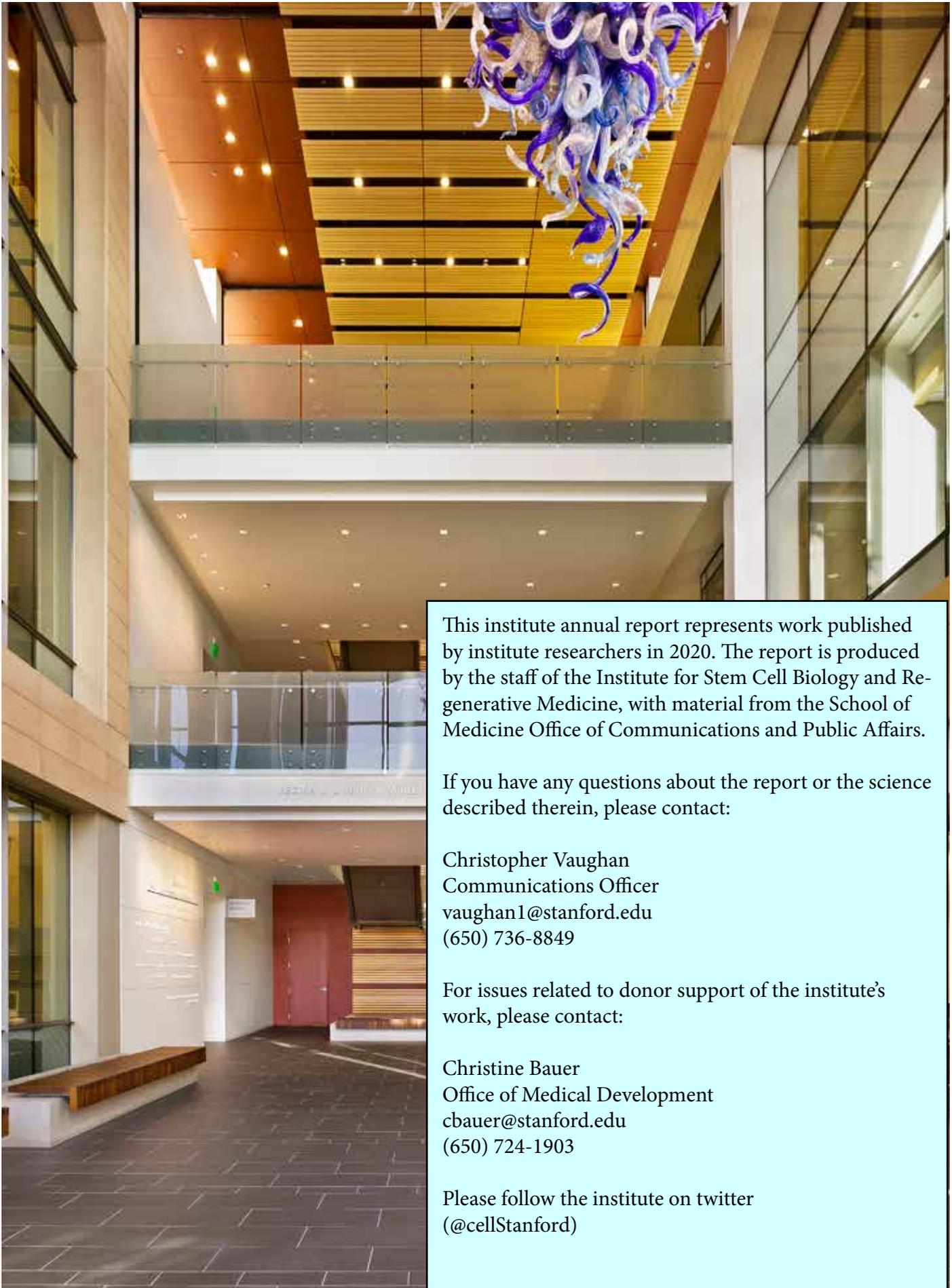


2020 ANNUAL REPORT

STANFORD INSTITUTE FOR STEM CELL BIOLOGY AND
REGENERATIVE MEDICINE

2020 ANNUAL REPORT

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Message From The Director

This message could be called ‘surviving 2020’, but that message certainly would not be unique to the institute. I assume all of us now see and are seen via Zoom or other venues like it, while we sit in our chairs countless hours, absent the closer interactions with colleagues, family, friends that sharing a room provides. As with all disasters, some entities will be irreversibly damaged, while others will survive or arise to provide discoveries or actions that allow them to emerge and contribute to

a better future. One of the things I hope we have learned is that ‘ground truths’ such as those provided by scientific discoveries and their translation,

rather than those based on misinformation or disinformation, can provide the way back. Here I want to emphasize that discoveries, linked to translation of those discoveries, can be critical to develop diagnoses and therapies to help the human condition.

To do so, I want to remind all of us of two precepts attributed to the Hippocratic oath, a version of which is taken as a pledge by all MD graduates around the world upon graduation (and at least at Stanford Medical School, by all biomedical graduates as well). This was the subject of my own address to the graduates of Stanford Medical School in 2002. The two precepts are:

- 1) Do no harm, and
- 2) Provide for all current and future patients the best therapies possible to ameliorate or eliminate their disease and/or medical condition.

As a pre-teenager in Great Falls, Montana, I read a book called *Microbe Hunters* by Paul de Kruif, written in 1927. The author wrote personalized accounts of the lives of discoverers of microbes such as Louis Pasteur, Robert Koch, Elie Metchnikoff, Paul Ehrlich, and others, who not only made breakthroughs, but who themselves translated those discoveries into practices such as finding and validating the disease-causing microbe, developing specific therapeutics for them, developing sanitation and public health methods to prevent their transfer,

When I entered Stanford Medical School, I kept hearing another mantra: “curiosity should be the (only?) driving force for biomedical scientists-- leave the translation to others.”

developing vaccination to bring in the elements of the immune response to protect against them, finding how some microbes use animals and insects

as intermediate vectors that pass infections into humans, etc.

Sound familiar? These are the critical issues of increasingly frequent microbial pandemics brought to us by planes, trains, boats, and cars. As the discoverers of these agents and the systems that protect us from them, these giants did not hesitate to

use their special knowledge from these discoveries to think about how they could be translated to medical practices that serve the patients they swore to protect when they took the Hippocratic oath.

That book started me on the career I have inhabited for the past 70 years. When I entered Stanford Medical School, I kept hearing another mantra: “curiosity should be the (only?) driving force for biomedical scientists-- leave the translation to others,” which at the time were the pharmaceutical companies. And that mantra today still holds potent force here and around the world. I agree that curiosity is an essential trait of biomedical scientists, but because they have opened fields that for days, weeks or years only they inhabit, I add the essential issue of thinking about how the discoveries might be translated for the benefit of patients, and taking responsibility that the translation is set in progress.

The Institute for Stem Cell Biology and Regenerative Medicine is a place where we try to discover fundamental processes, accepting that the many different types of stem cells (embryonic stem cells, tissue- and organ-specific stem cells, pre-cancer and cancer stem cells, and recently, disease-causing

rogue tissue and organ stem cells) are the irreducible units of biology, regeneration, and disease. No single gene or gene product, or mechanisms that regulate expression or silencing of single or suites of genes, are the units. Those molecules are the mechanisms used by the stem cells, as units, described here. So our scientists make both molecular and cellular discoveries, but all within the context of these self-renewing cells called stem cells.

No one should think that the translation of discoveries happens in a day. No one should claim that. While helping write and explain

Proposition 71 in 2004, and its successor Proposition 14 this year, I explained that if you counted back from the day a drug or antibody or stem cell therapy was approved as being safe and efficacious (in Hippocratic terms, “provide for patients the best and most advanced therapies”), to the day the initiation discovery was made, you will see a 10- to 20-year gap. This is because the final approval came from phase III clinical trials that took at least 3-5 years, which was preceded by a phase II clinical trial of at least 2-5 years (to show that a safe agent had the possibility of efficacy), and before that came the crucial phase I “first-in-human” clinical trials taking 1-3 years to find the doses of the agent that could be given safely to humans (to follow the first Hippocratic principle, “do no harm”).

Before one can do phase I trials, one must develop methods and practices to show a preclinical proof-

No one should think that the translation of discoveries happens in a day ...if you counted back from the day a drug or antibody or stem cell therapy was approved as being safe and efficacious ... to the day the initiation discovery was made, you will see a 10- to 20-year gap.

of-principle that the discovery can work in animal subjects, and can be delivered to these animals in a way such that the correct doses can be achieved

and maintained. From these studies, researchers must develop and file with the FDA or its equivalents the plans for a phase I study, which the agency has 30 days to either accept and allow, or reject. This preclinical phase can take 4-6 years to complete. And before that, there must be a discovery worth testing, which comes from curiosity-driven research.

An example from our institute: Ravi Majeti and I discovered that blocking antibodies to the cancer cell-surface protein CD47 allows

the immune system to attack and kill those cancer cells. I wrote a grant to the Proposition-71-funded California Institute for Regenerative Medicine (CIRM) to take anti-CD47 antibodies from discovery to phase I trials. The project was funded in 2010, and we the inventors formed a team with the aid of the then Stanford Cancer Center and the Ludwig Center at Stanford to carry out this phase in a not-for-profit academic setting. Within 4 years, Stanford sponsored a phase I trial for this project at Stanford and in the United Kingdom. Now, ten years after discovery, there are many clinical trials of anti-CD47 antibodies in process after successful phase II results in leukemia, myelodysplastic syndrome, and relapsed and treatment-refractory large-cell and follicular lymphomas. These trials are carried out not only by biotech/pharma entities licensed by Stanford, but also competitively by a large number of other cancer

companies, but that's another subject.

We are convinced that keeping the discoverers in preclinical development and phase

I trials greatly improved the chances for success, lowered the overall costs to get to and through these stages, and certainly accelerated their timeline. And as you will read in this report and others from the institute, this therapeutic now has preclinical proof-of-principle for a variety of diseases (including incurable fibrotic disorders such as lung, liver, post-surgical abdominal and pelvic cavity adhesions, and inherited fibrotic diseases)

and to understand and help eliminate persistent microbial infections hiding out inside cells, as well as atherosclerotic diseases that cause heart attack, stroke, aneurysms, diabetic loss of sight or limbs, etc.

In my view, this calls for a new paradigm of the discovery-to-clinical-application process, one that has force not only from our own work, but all over California. This paradigm includes developing

We are convinced that keeping the discoverers in preclinical development and phase I trials greatly improved the chances for success, lowered the overall costs to get to and through these stages, and certainly accelerated their timeline.

funding mechanisms to carry out the translation of discoveries at academic and nonprofit institutions led by the discoverers themselves with preclinical

and clinical trialists and regulatory experts, so that risk-diminished potential therapies can then be licensed to entities that can further develop and distribute those therapies.

While these potential therapies remain in academia through early clinical trials, the students, fellows, faculty and staff involved can remain true to the frankly idealistic goals first espoused in the Hippocratic oath.

In this annual report, you learn about several discoveries and the avenues you and the discoverers can think about whereby they might be translated. And with your help, they will be.

Yours,
Irv Weissman, MD
Director



Translational Stem Cell Research

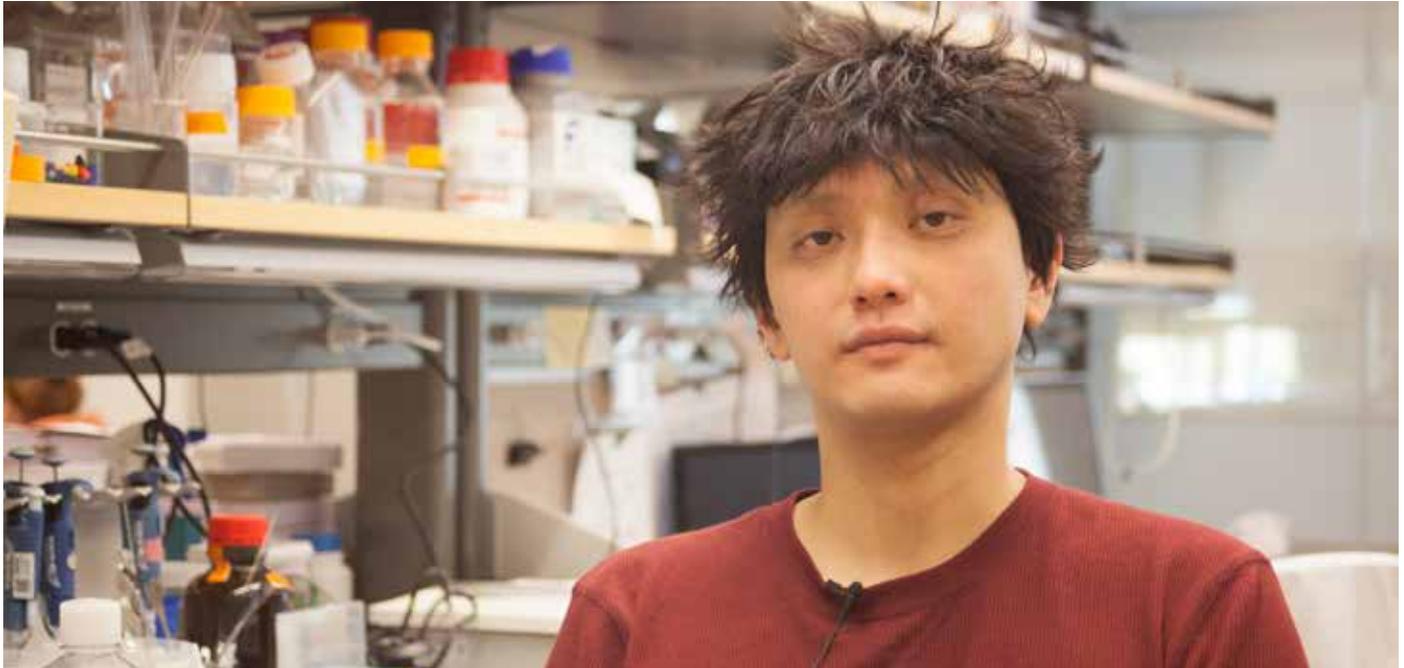
A major focus of the institute has always been the **translation** of stem cell research into **therapies** that can be used to treat human disease. Stem cell therapies offer the promise of **one-time treatments** that can **cure for life**.

This year, institute researchers discovered a method of growing true cartilage in damaged or aged joints. Painful and arthritic joints are one of the biggest public health complaints, and despite the widespread advertisement of “stem cell” treatments for joints, no other therapy has utilized skeletal stem cells.

Researchers also identified a stem cell mechanism that seems to be a major contributor to atherosclerosis, one of the main causes of human disability and death. The discovery may herald a new way to treat this killer disease.

Stanford researchers find a method to regrow cartilage in the joints

Degenerating or damaged cartilage causes joint pain and arthritis for hundreds of thousands of people. For the first time ever, researchers at Stanford have shown that true cartilage can be regrown from people's own stem cells.



Charles Chan, PhD

Researchers at the institute have discovered a way to regenerate, in mice and human tissue, the cushion of cartilage found in joints.

Loss of this slippery and shock-absorbing tissue layer, articular cartilage, is responsible for many cases of joint pain and arthritis, which afflicts over 55 million Americans. Currently, nearly 1 in 4 adult Americans suffer from arthritis, and far more are burdened by joint pain and inflammation generally. The Stanford researchers figured out how to regrow articular cartilage by first causing slight injury to the joint tissue, then using certain chemical signals to steer the growth of skeletal stem cells as the injuries heal. The work will be published Aug. 17 in the journal *Nature Medicine*.

“Cartilage has practically zero regenerative potential in adulthood, so once it’s injured or gone, what we can do for patients has been very limited,” said assistant professor of Surgery, Plastic and Reconstructive Surgery, Charles KF Chan, PhD. “It’s extremely gratifying to find a way to help the body regrow this important tissue.”

The work builds on previous research at Stanford

that resulted in isolation of the skeletal stem cell, a self-renewing cell that is also responsible for the production of bone, cartilage and a special type of cell that helps blood cells develop in bone marrow. The new research, like the previous discoveries of mouse and human skeletal stem cells, were mostly carried out in the laboratories of Chan and professor of surgery Michael Longaker, MD.

Articular cartilage is a complex and specialized tissue that provides a slick and bouncy cushion between bones at the joints. When this cartilage is damaged by trauma, disease or simply thins with age, bones can rub directly against each other, causing pain and inflammation, which can eventually result in arthritis.

Currently, damaged cartilage can be treated through a technique called microfracture, in which tiny holes are drilled in the surface of a joint. The microfracture technique prompts the body to create new tissue in the joint, but the new tissue is not much like cartilage.

“Microfracture results in what is called fibrocartilage, which is really more like scar tissue than natural cartilage,” said Chan. “It covers the bone and is better than nothing, but it doesn’t have the bounce and elasticity of natural cartilage, and tends to degrade relatively quickly.”

The current research arose in part through the work of surgeon Matthew Murphy, PhD, a visiting researcher at Stanford who is now at the University of Manchester. “I never felt anyone really understood how microfracture really worked,” Murphy said. “I realized the only way to understand the process was to look at what stem cells are doing after



Michael Longaker, MD

microfracture.” Murphy is the lead author on the paper. Chan and Longaker are co-senior authors. For a long time, Chan said, people assumed that adult cartilage did not regenerate after injury because the tissue did not have many skeletal stem cells that could be activated. Working in a mouse model, the

team documented that microfracture did indeed activate skeletal stem cells. Left to their own devices, however, those activated skeletal stem cells regenerated fibrocartilage in the joint.

But what if the healing process after microfracture could be steered toward development of cartilage and away from fibrocartilage? The researchers knew that as bone develops, cells must first go through a cartilage stage before turning into bone. They therefore had the idea that they might encourage the skeletal stem cells in the joint to start along a path toward becoming bone, but stop the process at the cartilage stage.

The researchers used a powerful molecule called bone morphogenetic protein 2 (BMP2) to initiate bone formation after microfracture, but then stopped the process midway with a molecule that blocked another signaling molecule important in bone formation called vascular endothelial growth factor (VEGF).

“What we ended up with was cartilage that is made of the same sort of cells as natural cartilage with comparable mechanical properties, unlike fibroblastic fibrocartilage that we usually get.” Chan

said. “It also restored mobility to osteoarthritic mice and significantly reduced their pain.”

As a proof of principle that this might also work in humans, the researchers transferred human tissue into mice that were bred to not reject the tissue, and were able to show that human skeletal stem cells could be steered toward bone development but stopped at the cartilage stage.

The next stage of research is to conduct similar experiments in larger animals before starting human clinical trials. Murphy points out that because of the difficulty in working with very small mouse joints, there might be some improvements to the system they could make as they move into relatively larger joints.

The first human clinical trials might be for people who have arthritis in fingers and toes. “We might start with small joints, and if that works we would move up to larger joints like knees,” Murphy says. “Right now, one of the most common surgery for arthritis in the fingers is to have the bone at the base of the thumb taken out. In such cases we might try this to save the joint, and if it doesn’t work we just take out the bone as we would have anyway. There’s a big potential for improvement, and the downside is that we would be back to where we were before.”

Longaker points out that one advantage of their discovery is that the main components of a potential therapy are already approved as safe and effective by the FDA. “BMP2 has already been approved for helping bone heal, and VEGF inhibitors are already used as anti-cancer therapies,” Longaker said. “This would help speed the approval of any therapy we develop.”

Joint replacement surgery has revolutionized how doctors treat arthritis and is very common: By age 80, 1 in 10 people will have a hip replacement and 1 in 20 will have a knee replaced. But such joint replacement is extremely invasive, has a limited lifespan and is performed only after arthritis hits and patients endure lasting pain. The researchers say they can envision a time when people are able to avoid getting arthritis in the first place by rejuvenating their cartilage in their joints before it is badly degraded.

“One idea is to follow a ‘Jiffy Lube’ model of cartilage replenishment,” Longaker said. “You don’t wait for damage to accumulate — you go in periodically and use this technique to boost your articular cartilage before you have a problem.”

Unregulated artery cell growth may drive atherosclerosis, Stanford Medicine research shows

Unregulated cell growth seems to be a driver behind the growth of atherosclerotic plaques, changing the traditional story of plaque formation. The rapid cell growth in the arterial wall is similar to pre-cancerous growth in other tissues

For decades, the standard story of how atherosclerotic plaque forms focused on the accumulation of cholesterol and inflammatory cells in arterial walls. Now, researchers at the Stanford University School of Medicine have identified another factor that initiates the formation of these plaques: inflamed smooth muscle cells in the linings of arterial walls that multiply in an unregulated way.

The culprit behind many heart attacks and strokes, atherosclerotic plaques are unhealthy masses of oxidized cholesterol, immune cells and dead tissue that form within arterial walls. When atherosclerotic plaques grow very large or rupture they can impede blood supply to vital tissues and organs, making them a lethal threat.

“The combination of hyper proliferative grow and increased expression of ‘don’t eat me signals ... give these cells a competitive advantage over normal cells.”

“Cardiovascular disease remains the world’s No. 1 killer, despite widespread use of cholesterol-lowering medicines,” said Nicholas Leeper, MD, professor of surgery at Stanford. “Recent studies have indicated that the standard dogma about how atherosclerosis happens wasn’t really capturing the whole story.” In 1973, researchers proposed that a substantial portion of atherosclerotic plaques were made up of arterial blood vessel cells that had expanded over time, and that these abnormally growing cells could be driving the growth of the plaque. But for decades, that idea was sidelined in favor of findings pointing to the importance of cholesterol in plaque formation.

Renewed interest in old finding

Recently, Leeper and his colleagues renewed their interest in the old finding. They demonstrated that these abnormal blood vessel cells were protected from removal by the immune system, indicating that the cells could be part of the disease process underlying plaque formation.

To find out how these rapidly proliferating cells arise, sparking the chain of events that leads to plaque formation, Leeper and his colleagues looked at blood vessel muscle cells in a plaque using “rainbow” mice; these mice can be triggered so that every cell in their bodies expresses a particular color of a fluorescent protein. A single cell can be marked the color red, for instance. As it and its offspring divide, all the exact copies, or clones, that arise will colored red. The researchers showed that very early in the formation of a plaque, a single cell in the smooth muscle cell layer of the artery starts to proliferate more than it should, leading to the growth of a lesion in the vessel wall that can constrict blood flow.

Normally, such poorly regulated cell growth could be controlled by immune cells that eat the outlaw cells. But in addition to losing regulatory features that control cell growth, the smooth muscle cells arm themselves with CD47, a cell marker that gives off a “don’t eat me” signal to immune cells.

“The combination of hyperproliferative growth and increased expression of ‘don’t eat me’ signals that frustrate immune mechanisms that would otherwise control them give these cells a competitive advantage over normal smooth muscle cells,” Leeper said.

A paper describing the research was published in June in the Proceedings of the National Academy of Sciences. Leeper is the senior author. Postdoctoral



Nicholas Leeper, MD, PhD

fellow Ying Wang, PhD, is the lead author. Institute director Irv Weissman, MD is a co-author.

‘Spewing out inflammatory factors’

Leeper and his colleagues identified an additional characteristic of these rogue cells that leads to plaque formation. “The cells are not only proliferating in an uncontrolled way, they are also spewing out inflammatory factors,” Leeper said. When the researchers

“If we block the CD47 signalling, these plaques start to go away.”

looked at the genes turned on and off in proliferating cells, they found that they produced high levels of a molecule called C3, a key part of the immune system that pumps up immune activity and inflammation. A systemic increase in C3 is known to be a risk factor in cardiovascular disease.

Moving beyond the mouse model and into human patients, they confirmed that C3 production is increased in a subset of smooth muscle blood vessel cells in human plaques.

Finally, the researchers analyzed plaque samples from patients with coronary artery disease and confirmed that human plaques had cells that had very similar gene expression profiles as the plaque-initiating smooth muscle cells in the mouse model.

“This research confirms that plaques are founded on a clone of arterial smooth muscle cells that are rapidly dividing, evading immune control, and producing prodigious amounts of pro-inflammatory signals,” Leeper said.

The unregulated clonal expansion of cells in atherosclerotic plaques parallels that of poorly regulated cell growth in cancerous or pre-cancerous tissues, the researchers say.

“The clonal expansion of smooth muscle cells looks a lot like what we find in other pre-cancerous diseases like myelodysplastic syndrome,” which is caused by a clone of blood-forming stem cells taking over the blood forming system, said professor Irving Weissman, MD, a co-author on the paper and the Virginia and DK Ludwig Professor for Clinical Investigation in Cancer Research. “In theory, given enough time, this might become a cancer of the arteries, but it kills people through plaque formation long before that.”

Similarity to cancer cells

Cancer cells exhibit the same increase in CD47 “don’t eat me” signals that prevent them from being consumed by immune cells. Research in Weissman’s laboratory and evidence from clinical trials have shown that blocking the CD47 signal leads the immune system to attack cancer cells, and Leeper’s group has shown that blocking CD47 could also lead to reduction in the size of atherosclerotic plaques.

“If we block the CD47 signaling, these plaques start to go away,” Leeper said. There is currently no FDA-approved therapy to block CD47 signaling, but anti-CD47 therapies are in clinical trials as a cancer therapy. Clinical trials of anti-CD47 therapy against atherosclerosis are likely to follow, Leeper said.

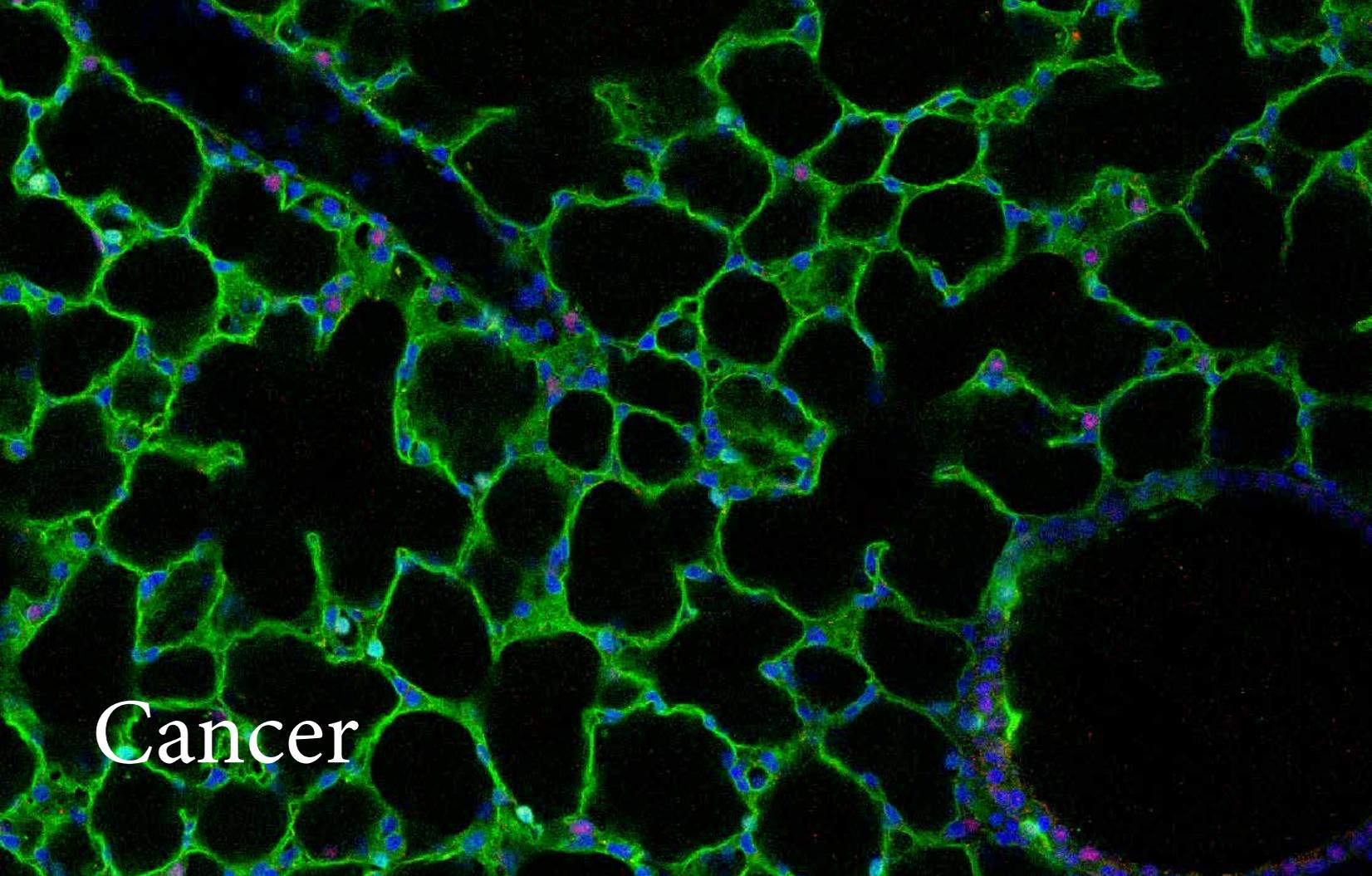
Researchers are also still working to understand how the unregulated blood vessel cell growth relates to the accumulation of cholesterol and other materials



Irv Weissman, MD

in plaques.

Leeper says that the proliferative smooth muscle cell model of atherosclerotic plaque formation has implications that point to other possible treatments. “These multiplying cells can give rise to different varieties of smooth muscle cell, some bad and some good,” Leeper said. “In the future we may be able to bias the reproduction of these cells away from the bad, toward the good.”



Cancer

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

This year, in addition to new and continuing **clinical trials** of innovative cancer therapies, institute researchers have advanced our understanding of how cancers arise, how to diagnose and analyze them, and how better to treat them.

A single number helps Stanford data scientists find the most dangerous cancer cells



Aaron Newman, PhD

Stanford data scientists have found a metric that indicates which cancer cells are genetically closest to stem cells, which makes them more dangerous

Biomedical data scientists at the institute have shown that the number of genes a cell uses to make RNA is a reliable indicator of how developed the cell is, a finding that could make it easier to target cancer-causing genes.

Cells that initiate cancer are thought to be stem cells, which are hard-to-find cells that can reproduce themselves and develop, or differentiate, into more specialized tissue, such as skin or muscle — or, when they go bad, into cancer.

“Right now, targeted therapies are focused on specific genes or molecules, the vast majority of which may not be specific to cancer stem cells,” said Aaron Newman, PhD, assistant professor of Biomedical Data Science and a member of the Institute for Stem Cell Biology and Regenerative Medicine. “Usually these therapies don’t work for very long. But if you can identify the least-differentiated cells and then look for markers specific to them, it’s no longer a guessing game to find the genes to target.”

The study’s finding is also significant because identifying stem cells of various tissue types is an important step toward regenerating damaged or malfunctioning tissues.

What the scientists showed is that as stem cells become more differentiated and more like adult cells, they express fewer and fewer genes. Previously, other researchers had noticed this correlation and thought it might be an interesting coincidence. But Newman and his colleagues were the first to sort through thousands of single-cell genetic tests in public databases and prove this pattern was consistent and reliable.

Newman and MD-PhD student Gunsagar Gulati combined the measurement of the number of genes expressed in a cell with the measurement of the number of RNA copies created per gene as the basis for a computer algorithm, CytoTRACE, designed to determine how developmentally advanced cells are. A paper describing the research was published this year in the journal *Science*. Newman is the senior author. Gulati and Shaheen Sikandar, PhD, an instructor at the institute, share lead authorship. Cancerous tumors can contain many millions of cells, each of which may have thousands of gene mutations. The cells in a tumor are diverse. Most will be differentiated cells that die out naturally on their own, while relatively few are the more

dangerous cancer stem cells, or tumor-initiating cells. These cells are hard to find and therefore hard to characterize using current methods, but far easier to find with CytoTRACE.

“As a cancer researcher, what I find most exciting is that this tool helps us find the tumor-initiating cells that have long been known to be responsible for resistance to treatment, metastasis and relapse after treatment,” Sikandar said.

Michael Clarke, MD, one of the authors of the paper, was the first researcher to identify cancer stem cells in a solid tumor. A professor of medicine at Stanford, Clarke said that CytoTRACE, which analyzes data on all the RNA created in a single cell, can

“As a cancer researcher, what I find most exciting is that this tool helps us find the tumor-initiating cells that have long been known to be responsible for resistance to treatment, metastasis and relapse after treatment”

quickly recapitulate research that takes years using traditional methods. “The way that we currently find cell markers for cancer stem cells is to make educated guesses about which markers will likely be important, then sort those cells and look for stem cell activity,” said Clarke, the Karel H. and Avicenne N. Beekhuis Professor in Cancer Biology and associate director of the Institute for Stem Cell Biology and Regenerative Medicine.

Researchers can look at relatively few markers at a time, so it takes a lot of sorting and analysis, and in the end, they will likely be only partially successful in finding good markers of the stem cells they are looking for, he said. “What CytoTRACE allows us to do is first find the stem or progenitor cells, then look at what unique markers they have on them.”

In the paper, the researchers describe using CytoTRACE to query single-cell RNA data for triple-

negative breast cancer, a type of tumor that is rarer but more dangerous because tumor growth doesn't rely on the biochemical pathways that physicians usually target to treat breast cancer. Not only did CytoTRACE identify known markers of cancer stem cells, it also spotted a marker that had not been previously been thought to be important. “This one gene looks like it has amazing potential as a therapeutic,” Clarke said.

CytoTRACE also has the potential to transform how researchers hunt for stem cells associated with other diseases, Newman said. “This tool could also be useful in finding treatments for disorders such as Alzheimer's or other degenerative diseases where loss of stem cell function might be part of the disease process,” he said.

Regenerative medicine, in which diseased or damaged tissue is repaired through the activity of stem cells, requires the ability to isolate purified populations of stem cells specific to a given tissue. To regrow bone, the heart or the eyes, for example, researchers must first find the stem cells responsible for regrowing those organs. Finding the markers that are specific to these normal stem cells has been much like the process for finding cancer stem cell markers, the researchers say — that is, the product of educated guesses, luck and a lot of work in the lab. CytoTRACE could significantly shorten that process.

“One of the main motivations behind developing CytoTRACE was to create a tool for rapid and accurate identification of stem cells in humans,” Gulati said. “But another important question we hope to answer is how the inner workings of a cell change as the cell transforms from one state to another. This research opens up a whole new avenue of research to study how global changes in gene expression and DNA structure influence a cell's state.”

Overall, Newman said, the study shows the power and promise of using big data to advance biology and medicine through computer research that complements discoveries made in the lab.

“It wouldn't have been possible to gather all this data in our lab, but by using public databases and asking the right questions, it's more and more possible to make fundamental discoveries in biology and medicine,” he said.

Stanford researchers program cancer-fighting cells to resist exhaustion, attack solid tumors in mice

CAR-T cells are remarkably effective against blood cancers, but their effect can be transient as the cells become exhausted. Stanford researchers found a way to keep the cells effective in mice with human tumors

Institute member Michelle Monje, MD, PhD collaborated with Stanford Cancer Institute researchers to find a new approach to programming cancer-fighting immune cells called CAR-T cells to prolong their activity and increase their effectiveness against human cancer cells grown in the laboratory and in mice.

The ability to circumvent the exhaustion that the genetically engineered cells often experience after their initial burst of activity could lead to the development of a new generation of CAR-T cells that may be effective even against solid cancers — a goal that has until now eluded researchers.

“Those of us in the CAR-T cell field have wondered for some time if these cells could also be used to combat solid tumors.”

The studies were conducted in mice harboring human leukemia and bone cancer cells. The researchers hope to begin clinical trials in people with leukemia within the next 18 months and to eventually extend the trials to include solid cancers.

“We know that T cells are powerful enough to eradicate cancer,” said Crystal Mackall, MD, professor of pediatrics and of medicine at Stanford and the Ernest and Amelia Gallo Family Professor. “But these same T cells have evolved to have natural brakes that tamp down the potency of their response after a period of prolonged activity. We’ve developed a way to mitigate this exhaustion response and improve the activity of CAR-T cells against blood

and solid cancers.”

Mackall, who is also the director of the Stanford Center for Cancer Cell Therapy and of the Stanford research center of the Parker Institute for Cancer Immunotherapy, treats children with blood cancers at the Bass Center for Childhood Cancer and Blood Diseases at Stanford Children’s Health.

Mackall is the senior author of the study, which was published in the journal *Nature*. Former postdoctoral scholar Rachel Lynn, PhD, is the lead author. Monje is one of the coauthors.

Genetically modified cells of patient

CAR-T cells is an abbreviation for chimeric antigen receptor T cells. Genetically modified from a patient’s own T cells, CAR-T cells are designed to track down and kill cancer cells by recognizing specific proteins on the cells’ surface. CAR-T cell therapy made headlines around the world in 2017 when the Food and Drug Administration fast-tracked their approval for the treatment of children with relapsed or unresponsive acute lymphoblastic leukemia. Later that year, a version of CAR-T treatment was also approved for adults with some types of lymphoma. But although blood cancers often respond impressively to CAR-T treatment, fewer than half of treated patients experience long-term control of their disease, often because the CAR-T cells become exhausted, losing their ability to proliferate robustly and to actively attack cancer cells. Overcoming this exhaustion has been a key goal of cancer researchers for several years.

Lynn and Mackall turned to a technique co-developed in the laboratory of Howard Chang, MD, PhD, the Virginia and D.K. Ludwig Professor of Cancer Genomics and professor of genetics at Stanford, to understand more about what happens when T cells become exhausted and whether it might be possible to inhibit this exhaustion. The



Michelle Monje, PhD

technique, called ATAC-Seq, pinpoints areas of the genome where regulatory circuits overexpress or underexpress genes.

“When we used this technique to compare the genomes of healthy and exhausted T cells,” Mackall said, “we identified some significant differences in gene expression patterns.” In particular, the researchers discovered that exhausted T cells demonstrate an imbalance in the activity of a major class of genes that regulate protein levels in the cells, leading to an increase in proteins that inhibit their activity.

Attacking solid tumors

When the researchers modified CAR-T cells to restore the balance by overexpressing c-Jun, a gene that increases the expression of proteins associated with T cell activation, they saw that the cells remained active and proliferated in the laboratory even under conditions that would normally result in their exhaustion. Mice injected with human leukemia cells lived longer when treated with the

modified CAR-T cells than with the regular CAR-T cells. In addition, the c-Jun expressing CAR-T cells were also able to reduce the tumor burden and extend the lifespan of laboratory mice with a human bone cancer called osteosarcoma.

“Those of us in the CAR-T cell field have wondered for some time if these cells could also be used to combat solid tumors,” Mackall said. “Now we’ve developed an approach that renders the cells exhaustion resistant and improves their activity against solid tumors in mice. Although more work needs to be done to test this in humans, we’re hopeful that our findings will lead to the next generation of CAR-T cells and make a significant difference for people with many types of cancers.”

Cell growth clue could lead to new breast cancer treatments

Researchers at the Stanford Institute for Stem Cell Biology and Regenerative Medicine have discovered a molecule that can fuel the growth of breast cancer cells and, if blocked, offers a potential avenue for attacking breast cancer.

The discovery may be especially useful for “triple negative” breast cancers that don’t currently offer a good target for therapy, the researchers said.

The molecule, called LEFTY1 by the researchers, plays a beneficial role in normal breast tissue remodeling that happens in response to changing hormonal cycles. However, it can also be used to promote out-of-control growth in breast cancer cells. “A normal function of this molecule has been hijacked by the cancer cells to allow them to replicate unchecked,” said Michael Clarke, MD, the associate director of the institute and senior author of a paper recently published on the research in *Cell Stem Cell*.

Blocking the signal from LEFTY1

LEFTY1 inhibits other molecules that change stem cells into more mature or “differentiated” cells. As cells mature, they lose their ability to make more of themselves.

“What we discovered is that when stem and progenitor cells are stopped from specializing, they default to a program of reproducing themselves,” said Neethan Lobo, PhD, a co-lead author on the paper and a former postdoctoral scholar in the Clarke lab. “It’s like if you stopped someone from becoming an adult, they stay a kid forever.”

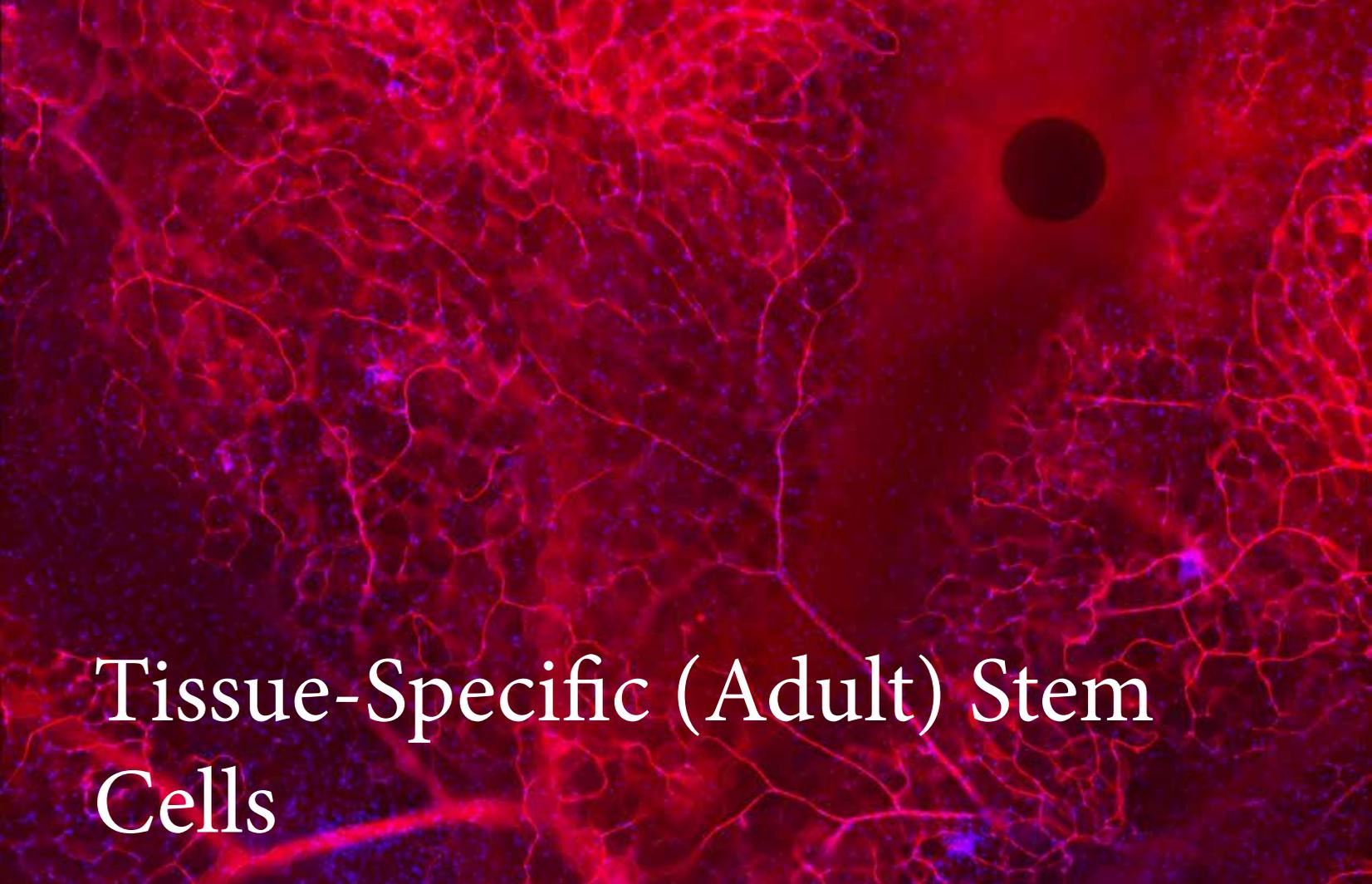
Two facts about LEFTY1 make it exciting for researchers. “One thing we saw is that the tumor-initiating cells, sometimes called cancer stem cells, are exquisitely dependent on this molecule,” Lobo said. The researchers found that when they blocked the signal from LEFTY1, tumor-initiating cells in triple negative breast cancer tissue would stop growing.

The other exciting thing is that LEFTY1 affects cellular activity from outside the cell.

“A lot of things we look at are inside the cell, and are therefore not easily manipulated,” said Jane Antony, PhD, a co-lead author on the paper and a postdoctoral scholar in the Clarke lab. “But this is released outside the cells, which makes it much more accessible to drugs and therapies we might administer.”



Michael Clarke, MD

A fluorescence microscopy image showing a dense network of red-stained cells or fibers, with several blue-stained spots scattered throughout. A dark circular artifact is visible in the upper right quadrant.

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**.

Old human cells rejuvenated with stem cell technology

New research shows older human cells can undergo “rejuvenation” and begin acting like much younger versions of themselves

Old human cells can become more youthful by coaxing them to briefly express proteins used to make induced pluripotent cells, Stanford researchers and their colleagues have found. The finding may have implications for aging research.

Old human cells return to a more youthful and vigorous state after being induced to briefly express a panel of proteins involved in embryonic development, according to a new study by researchers at the Institute for Stem Cell Biology and Regenerative Medicine.

The researchers also found that elderly mice regained youthful strength after their existing muscle stem cells were subjected to the rejuvenating protein treatment and transplanted back into their bodies.

The proteins, known as Yamanaka factors, are commonly used to transform adult cells into induced pluripotent stem cells, or iPS cells. Induced pluripotent stem cells can become nearly any type of cell in the body, regardless of the cell from which they originated. They’ve become important in regenerative medicine and drug discovery.

The study found that inducing old human cells in a lab dish to briefly express these proteins rewinds many of the molecular hallmarks of aging and renders the treated cells nearly indistinguishable from their younger counterparts.

“When iPS cells are made from adult cells, they become both youthful and pluripotent,” said Vittorio Sebastiano, PhD, assistant professor of obstetrics and gynecology and the Woods Family Faculty Scholar in Pediatric Translational Medicine. “We’ve wondered for some time if it might be possible to simply rewind the aging clock without inducing pluripotency. Now we’ve found that, by tightly controlling the duration of the exposure to these protein factors, we can promote rejuvenation in multiple human cell types.”

Sebastiano is the senior author of the study, which was published this year in *Nature Communications*. Former graduate student Tapash Sarkar, PhD, is the lead author of the article.

“We are very excited about these findings,” said



Vittorio Sebastiano, PhD

study co-author Thomas Rando, MD, PhD, professor of neurology and neurological sciences and the director of Stanford’s Glenn Center for the Biology of Aging. “My colleagues and I have been pursuing the rejuvenation of tissues since our studies in the early 2000s revealed that systemic factors can make old tissues younger. In 2012, Howard Chang and I proposed the concept of using reprogramming factors to rejuvenate cells and tissues, and it is gratifying to see evidence of success with this approach.” Chang, MD, PhD, is a professor of dermatology and of genetics at Stanford.

Exposure to proteins

Researchers in Sebastiano’s laboratory make iPS cells from adult cells, such as those that compose skin, by repeatedly exposing them over a period of about two weeks to a panel of proteins important to early embryonic development. They do so by introducing daily, short-lived RNA messages into the adult cells. The RNA messages encode the instructions for making the Yamanaka proteins. Over time, these

proteins rewind the cells' fate — pushing them backward along the developmental timeline until they resemble the young, embryonic-like pluripotent cells from which they originated.

During this process the cells not only shed any memories of their previous identities, but they revert to a younger state. They accomplish this transformation by wiping their DNA clean of the molecular tags that not only differentiate, say, a skin cell from a heart muscle cell, but of other tags that accumulate as a cell ages.

Recently researchers have begun to wonder whether exposing the adult cells to Yamanaka proteins for days rather than weeks could trigger this youthful reversion without inducing full-on pluripotency. In fact, researchers at the Salk Institute for Biological

This is an opportunity to change how we think about the development of not just the skeleton, but also other tissues and organs.

Studies found in 2016 that briefly expressing the four Yamanaka factors in mice with a form of premature aging extended the animals' life span by about 20%. But it wasn't clear whether this approach would work in humans.

Sarkar and Sebastiano wondered whether old human cells would respond in a similar fashion, and whether the response would be limited to just a few cell types or generalizable for many tissues. They devised a way to use genetic material called messenger RNA to temporarily express six reprogramming factors — the four Yamanaka factors plus two additional proteins — in human skin and blood vessel cells. Messenger RNA rapidly degrades in cells, allowing the researchers to tightly control the duration of the signal.

The researchers then compared the gene-expression patterns of treated cells and control cells, both obtained from elderly adults, with those of untreated cells from younger people. They found that cells from elderly people exhibited signs of aging reversal after just four days of exposure to the reprogramming factors. Whereas untreated elderly

cells expressed higher levels of genes associated with known aging pathways, treated elderly cells more closely resembled younger cells in their patterns of gene expression.

When the researchers studied the patterns of aging-associated chemical tags called methyl groups, which serve as an indicator of a cell's chronological age, they found that the treated cells appeared to be about 1½ to 3½ years younger on average than untreated cells from elderly people, with peaks of 3½ years (in skin cells) and 7½ years (in cells that line blood vessels).

Comparing hallmarks of aging

Next they compared several hallmarks of aging — including how cells sense nutrients, metabolize compounds to create energy and dispose of cellular trash — among cells from young people, treated cells from old people and untreated cells from old people.

“We saw a dramatic rejuvenation across all hallmarks but one in all the cell types tested,” Sebastiano said. “But our last and most important experiment was done on muscle stem cells. Although they are naturally endowed with the ability to self-renew, this capacity wanes with age. We wondered, ‘can we also rejuvenate stem cells and have a long-term effect?’”

When the researchers transplanted old mouse muscle stem cells that had been treated back into elderly mice, the animals regained the muscle strength of younger mice, they found.

Finally, the researchers isolated cells from the cartilage of people with and without osteoarthritis. They found that the temporary exposure of the osteoarthritic cells to the reprogramming factors reduced the secretion of inflammatory molecules and improved the cells' ability to divide and function.

The researchers are now optimizing the panel of reprogramming proteins needed to rejuvenate human cells and are exploring the possibility of treating cells or tissues without removing them from the body.

“Although much more work needs to be done, we are hopeful that we may one day have the opportunity to reboot entire tissues,” Sebastiano said. “But first we want to make sure that this is rigorously tested in the lab and found to be safe.”

Infected cells send out a “don’t eat me” signal to suppress the immune response

Researchers at the Institute for Stem Cell Biology and Regenerative Medicine have discovered that cells infected by viruses or bacteria send out a “don’t eat me” signal to avoid attack by the body’s immune system.

Researchers at the institute, working with scientists at the National Institutes of Health, have discovered that cells infected by viruses or bacteria send out a “don’t eat me” signal to avoid attack by the body’s immune system.

After viruses and bacteria invade a human host, they are assisted by a molecule that dampens the immune response, researchers at the Stanford University School of Medicine have discovered. Strategies that suppress that immunological brake may help fight infectious disease.

The researchers showed that within 24 hours of a viral or bacterial infection, infected cells start expressing more of a molecule called CD47, a “don’t eat me” signal that prevents them from being engulfed by immune cells called macrophages. Stanford researchers previously discovered that cancer cells increase their expression of CD47, thereby evading attack from the immune system.

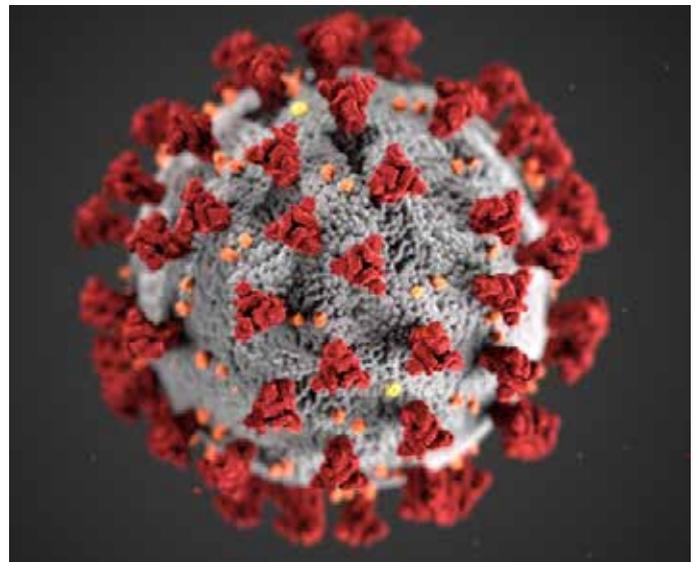
“We wondered whether the mechanism activated by all cancer cells to avoid being destroyed could also be used by persistent infections, so that the microbes can hide inside cells to evade immune cells,” said professor Irving Weissman, MD, director of the Institute for Stem Cell Biology and Regenerative Medicine and the Virginia and D. K. Ludwig Professor in Clinical Investigation in Cancer Research. “Amazingly, we found that to be true, and blocking the CD47 signal helped the body get rid of more infected cells.” The paper describing this research was published June 23 in the journal *mBio*. Weissman and Kim Hasenkrug, PhD, of the National Institutes of Health, are co-senior authors of the paper.

It has been known for some time that the response to infection by the adaptive immune system, which includes T and B cells, includes a mix of immune boosters and immune suppressors that rein in the immune system, ensuring it doesn’t overreact and cause more damage than the invading pathogen. For

instance, some flu or coronavirus patients are killed not by the activity of the viruses, but by a “cytokine storm,” a flood of immune signals released when the body can’t eliminate the virus. It’s a scorched earth defense by the immune system that can cause severe damage to healthy tissues.

CD47 regulates innate immune system

In the paper, the researchers showed that the very early response of the innate immune system, a more primitive but still important immunological system involving cells like macrophages, is also regulated by the immunologically suppressive CD47 molecule. Both mouse and human cells showed increased



Coronavirus model

expression of CD47 on their surfaces when infected by a pathogen, the researchers found. SARS-CoV-2, the coronavirus variant responsible for COVID-19, is one of the viruses that causes increased production of CD47, they said.

“It’s probably important for the innate immune system to have a balance of activating and suppressing forces, but pathogens seem to have co-opted this mechanism for their own purposes,” said Michal Tal, PhD, an instructor at the Institute for Stem Cell Biology and Regenerative Medicine and a lead author of paper. “We showed that if we play with that balance a little bit, we can clear some pathogens faster.”

To test whether negating the CD47 signal could boost the immune response to viruses, the scientists infected mice with a meningitis-causing virus called LCMV and gave some of them an antibody that blocks CD47. The mice given the antibody had significantly lower viral loads at all points in the experiment compared with the control group, which did not receive the antibody. The researchers also exposed a mouse missing the gene for CD47 to tuberculosis-causing bacteria. CD47-deficient mice showed significantly more resistance to infection by the bacteria and better survival compared with mice that could make CD47.

“It’s probably important for the innate immune system to have a balance of activating and suppressing forces, but we showed that if we play with that balance a little bit, we can clear some pathogens faster,” Tal said.

A possible new tactic

The researchers hope that manipulating the CD47 response to infection could be another tactic to fight viruses and bacteria. “In some cases, it might be better to ease up on this particular immunological brake by blocking CD47,” Tal said.

The approach is being tested on cancers such as leukemias, lymphomas and the pre-leukemic condition myelodysplastic syndrome. Cancer cells also made more CD47 as a way of suppressing the immune response that would attack them, and a therapeutic using antibodies to inhibit CD47 is already in clinical trials.



Michal Caspi Tal, PhD

Omega-3 fatty acids’ health benefit linked to stem cell control

A new finding by Stanford researchers represents a missing link between two worlds — that of dietary science, and that of molecular and cellular biology.

For years, researchers have known that defects in an ancient cellular antenna called the primary cilium are linked with obesity and insulin resistance. Now, researchers at the institute have discovered that the strange little cellular appendage is sensing omega-3 fatty acids in the diet, and that this signal is directly affecting how stem cells in fat tissue divide and turn into fat cells.

The finding represents a missing link between two worlds — that of dietary science, and that of molecular and cellular biology. Dietary studies have long found that the consumption of omega-3 fatty acids, essential fatty acids common in fish and nuts, is associated with lower risk of heart disease, stroke, arthritis and even depression.

A paper describing the research was published in the journal *Cell*. The senior author is Peter Jackson, PhD, professor of microbiology and immunology and of pathology. The lead author is postdoctoral scholar Keren Hilgendorf, PhD. Carl Johnson, PhD, a graduate student in the Stem Cell Biology and Regenerative Medicine program, was a co-author on the paper.

Looking for a signaling molecule

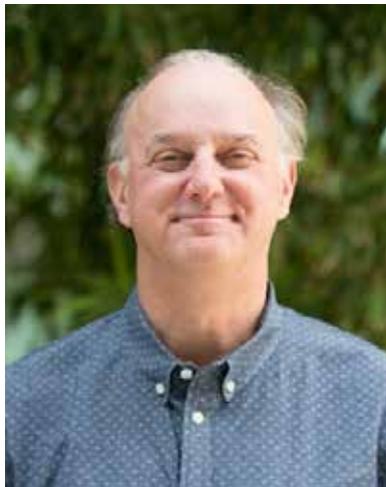
Researchers in Jackson’s laboratory weren’t looking for omega-3s when they started their research. They were looking only for the signaling molecule that fat stem cells were sensing. The molecule could have been anything: Signaling pathways in cellular biology often involve esoteric molecules few people have heard of. They knew only that in rare diseases involving a defect in the primary cilium, people are always hungry, cannot stop eating, and become obese and insulin resistant. So they were surprised when the signal turned out to be omega-3 fatty acids. “When we saw that the cell was responding to

omega-3 fatty acids, we realized that this had changed from just a molecular biology story to a story showing the molecular biology of how diet controls stem cells,” Jackson said.

The cells sense the presence of omega-3 fatty acids through a tiny, hair-like appendage called the primary cilium, an ancient structure derived from the many flagella that algae cells first used almost 1 billion years ago to move through the oceans and sense their surroundings. Over time, as single-celled organisms evolved into multicellular creatures that first swam the oceans and then crawled onto land, cells ditched most of their flagella. But most cells kept a single flagellum, the primary cilium, to use as a highly sensitive antenna; it can pick up extremely subtle signals about the world outside the cell, helping to regulate the cell’s function and fate.

Jackson and his colleagues found that when omega-3 fatty acids bind to a receptor called FFAR4 on the cilia of fat stem

cells, it prompts the fat stem cells to divide, leading to the creation of more fat cells. This provides the body with more fat cells with which to store energy, something that is healthier than storing too much fat in existing fat cells. “What you want is more, small



Peter Jackson, PhD

fat cells rather than fewer, large fat cells,” Jackson said. “A large fat cell is not a healthy fat cell. The

center is farther away from an oxygen supply, it sends out bad signals and it can burst and release toxic contents.” Large fat cells are associated with insulin resistance, diabetes and inflammation, he added.

Furthermore, the researchers found that the presence of saturated fats or the blockage of ciliary signaling of the FFAR4 receptor does not lead to an increase in the creation of new fat cells from stem cells, but rather the addition of fat to existing cells. “Rather than looking how diet correlates with health, we have gone from molecule to receptor to cell to document why ‘healthy fats’ are beneficial and ‘unhealthy fats’ contribute to disease,”

Hilgendorf said.

“We have provided a mechanism explaining why omega-3 fatty acids are critical for maintaining healthy fat balance and saturated fats should be limited.”

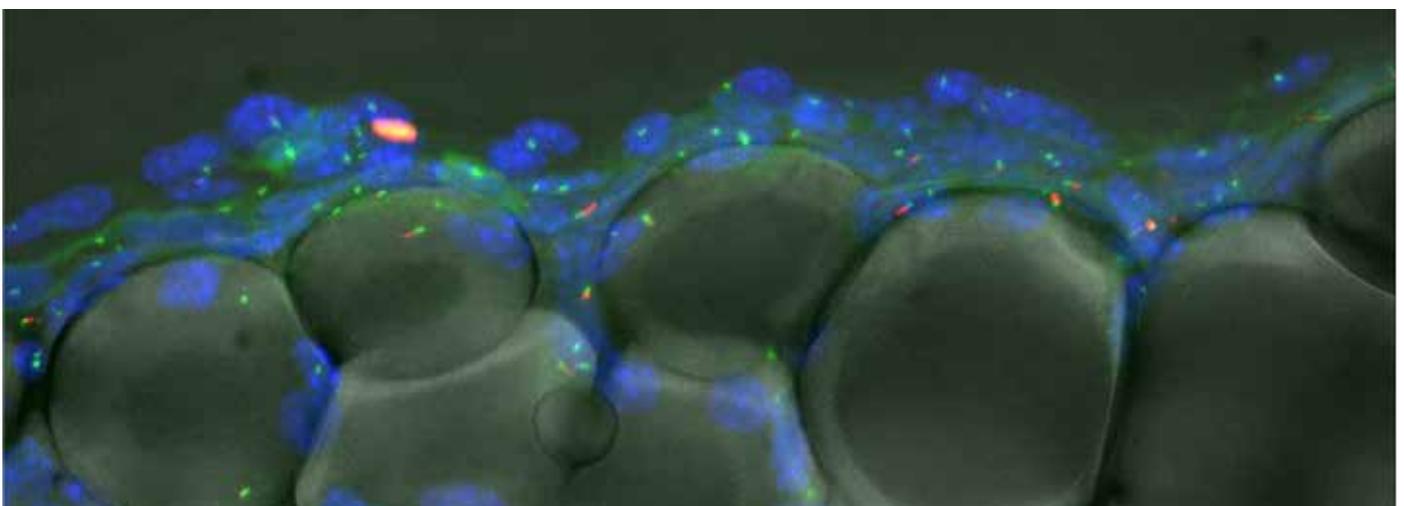
The research also may change scientific

understanding

of how the body manages fat storage in a healthy person. “Researchers often talk about the movement of fat in and out of cells, but what we are showing is the importance of stem cell activity in creating new fat cells as being critical for the body’s energy management,” said Johnson.



Carl Johnson, PhD



Honors

Roeland Nusse receives Canada's Gairdner International Award

Institute researcher Roeland Nusse, PhD, was honored for a lifetime of work on the Wnt (pronounced “wint”) signaling pathway, which plays an important role in normal stem cell activity and in cancer. Nusse, a professor of developmental biology, was the recipient of Canada's Gairdner International Award for his work on understanding the role of the Wnt signaling pathway in normal development and in cancer. The Wnt pathway is made up of a number of proteins, including one called Wnt, that transmit signals from outside the cell to the inside to trigger biological functions including gene expression and cell division.

The award recognizes excellence in fundamental research that affects human health.

Recipients receive 100,000 Canadian dollars (about \$72,000) to use as they wish; Nusse plans to donate his award to UNICEF to help provide protective equipment for health care workers caring for children amid the global COVID-19 pandemic. Nusse is the Reed-Hodgson Professor of Human Biology and the Virginia and Daniel K. Ludwig Professor in Cancer Research.

“What we're going through now is in many ways shocking,” Nusse said of the pandemic. “The fundamental problem facing humans now is biomedical in nature. When one receives an award for biomedical research, it makes you think, ‘Can I now make an impact that goes beyond my own work to meet an urgent global need?’ I would find it difficult to accept



Roeland Nusse, PhD

the prize money in the context of current events.” In 1982, Nusse collaborated with Harold Varmus, MD, then a professor in microbiology and immunology at the University of California-San Francisco, to identify Wnt as a critical cancer-associated gene in a mouse model of breast cancer. Nusse went on to show that the analogous gene in fruit flies, *Wingless*, plays an important role in regulating normal development. The finding highlighted the connections between normal development and cancer. More recently, Nusse has focused his research on understanding how Wnt signaling regulates the activity of tissue-specific adult stem cells in response to injury or disease. In 2016, Nusse was awarded a \$3 million Breakthrough Prize for his work on Wnt signaling. “It's very exciting to be recognized for a body of work, particularly by the Gairdner Foundation, which has such an impressive list of previous recipients,” Nusse said.

Institute Leadership



Irving Weissman, MD

Institute 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) stem 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, MD

Co-Director

George D. Smith Professor in Stem Cell and Regenerative Medicine

Maria Grazia Roncarolo 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.

Natalia Gomez-Ospina joins the institute

Dr. Gomez-Ospina is the newest member of the institute. She is an assistant professor of pediatrics specializing in genetics and stem cell transplantation.

Gomez-Ospina was born and raised in Medellin, Colombia. She began her undergraduate studies in petroleum engineering at the Universidad Nacional de Colombia before moving to Colorado. She double majored at the University of Colorado Boulder, completing her bachelor's degree in molecular cellular and developmental biology as well as biochemistry. She graduated summa cum laude and wrote an honors thesis entitled "Role of the quiescent center in the regeneration of the root cap in *Zea Mays*." She then completed her combined MD, PhD at Stanford Medical School, where her PhD work focused on understanding the novel functions of voltage-gated calcium channels. Her PhD thesis, "The calcium channel CACNA1C gene: multiple proteins, diverse functions," was published in *Cell*. After completion of her dual degrees, she did her preliminary year in internal medicine at Santa Barbara Cottage hospital before starting residency in Dermatology at Johns Hopkins Hospital. She completed residency in Medical Genetics at Stanford Hospital and clinics.

Gomez-Ospina's post-doctoral research was with Dr. Matthew Porteus in Pediatric Stem Cell transplantation, where she began to develop genome editing-based strategies in stem cells as a



Natalia Gomez-Ospina, PhD

therapies for metabolic diseases. She is currently an Assistant Professor in the Department of Pediatrics. For her clinical practice she sees patients with suspected genetic disorders, and is also in charge of the enzyme replacement service for lysosomal storage disorders at Lucile Packard Children's hospital. She has been the lead author in research studies in *The New England Journal of Medicine*, *Cell*, *Nature Communications*, and *American Journal of Medical Genetics*.

Around the Lorry Lokey Stem Cell Research Building, Gomez-Ospina is noticed by many for the neon "Gene Repair Shop" sign visible through her office window.



SCBRM Graduate Program

The 2020 entering class of SCBRM grad students

Stem Cell Biology and Regenerative Medicine Graduate Program

Ph.D. Class of 2020 – 2021

Jessica Arozqueta Basurto



During my undergraduate studies at the University of California Santa Cruz, I conducted research in Dr. Bin Chen's laboratory. There I studied how molecular mechanisms control the transition in radial glia cells from generating cortical excitatory neurons to olfactory bulb interneuron. I then went on to complete a master's at San Francisco State University as a California Institute for Regenerative Medicine (CIRM) Bridges fellow. While a CIRM scholar, I conducted my research under the mentorship of Dr. Alvarez-Buylla at the University of California San Francisco. My research focused on studying the cellular composition of the ventricular-subventricular zone with the goal of identifying populations of neural stem cells in the postnatal human brain. At Stanford, I hope to contribute to the development of clinical therapeutics to address neurodevelopmental disorders. Outside of the lab, I like to engage in activities like hiking, dancing, painting, and trying out new food cuisines.



Jeremy Bjelajac

I am originally from Los Angeles and graduated from Seattle University in 2018 with a BS in Cell and Molecular Biology. I spent the last two years working as a researcher in Dr. Michael Jensen's lab at Seattle Children's developing CAR T cell therapies for clinical pediatric cancer trials. I'm super interested in synthetic biology, specifically cellular engineering and rewiring cellular responses. I also love cooking, coffee, fashion, running, and just being outside.

Stem Cell Biology and Regenerative Medicine Graduate Program

Ph.D. Class of 2020 – 2021



Hana Ghanim

I am originally from Los Angeles, but I've been living in the Bay Area my entire adult life. I graduated from UC Berkeley with a degree in Molecular and Cell Biology in 2017 and spent a couple of years working on gene editing research at the Gladstone Institutes. As a graduate student, I am interested in using gene editing technology to generate therapies for inherited diseases. I love drinking good coffee, cooking new foods, and binge-watching TV.



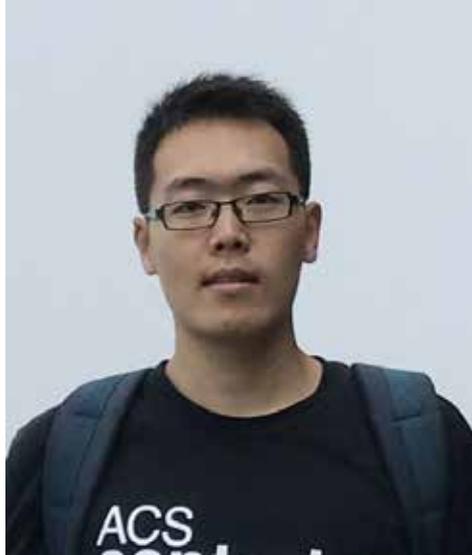
Archana Shankar

I graduated with a B.S in Molecular Biology and Biotechnology from California State University, Fullerton and worked to identify and characterize a minimal functional RNA splicing regulatory protein, PTBP1 (Keppetipola Lab). I was also fortunate to work as a CIRM intern at Stanford to understand the similarities and differences of bacterial and viral infection on neural stem and progenitor cells during neurodevelopment (Palmer Lab). Following graduation, I used induced pluripotent stem cells to develop cortical neurons, microglia, and 3-D cortical brain organoids to model autism spectrum disorders (Yeo Lab at University of California, San Diego). As a graduate student in the Stem Cell Biology and Regenerative Medicine Biology program at Stanford, I hope to expand on my interests in neurodevelopment and neurodevelopmental disorders and explore the interactions of different

cell types (neurons, astrocytes, oligodendrocytes, microglia) during development and disease. Outside the lab, I enjoy naps with my dog, baking, rock climbing, surfing, hiking, traveling, and being in the company of friends and family.

Stem Cell Biology and Regenerative Medicine Graduate Program

Ph.D. Class of 2020 – 2021



Peter (Sicong) Wang

I grew up in a small city, Baotou, in China. I graduated in 2016 with a BE in Biomedical Engineering. Then I received a master's degree in Mechanical Engineering from University of Michigan in 2019. During my time at Umich, I worked with Dr. Jianping Fu using a bio-engineered hPSC-based embryoid model to study early human development. During that time I developed a strong interest in stem cell biology. At Stanford, I am interested in studying the mechanisms of gene regulation in the context of human development. I am also very interested in adult tissue stem cells and potential applications in regenerative medicine. Outside of the lab, I enjoy hiking and biking to explore the national parks around the Bay Area. I also love cooking traditional Chinese food and exploring all kinds of Asian cuisines.



Maya Weigel

I grew up in the Bay Area and attended Pomona College where I received my BA in Biology. As a student-athlete at Pomona, I enjoyed running (literally) between the track and the lab. Before joining the Stem Cell Biology and Regenerative Medicine program, I worked in Dr. Ben Barres's lab at Stanford, where I primarily studied the role of neurotoxic reactive astrocytes in ALS and was drawn into the captivating world of glia. As a Stanford student, I hope to unite my interests in neural and glial development with cutting-edge advances in regenerative medicine to discover therapeutic solutions to neurological diseases. Outside of the lab, you can still catch me running lots of miles, basking in my beloved Bay Area sunshine, and finding new ways to use up my garden tomatoes.

Stem Cell Biology and Regenerative Medicine Graduate Program

M.D./Ph.D. Class of 2020 – 2021



Quenton Bubb

I am a Medical Scientist Training Program (MSTP) student from Brooklyn, New York. I received my B.A. in Biophysics in 2016 from Johns Hopkins, and subsequently got an MPhil in Chemistry at the University of Cambridge. While my undergraduate and MPhil research focused on protein folding kinetics and thermodynamics, my interests have shifted toward stem cell biology and cell therapies. At Stanford I will be exploring cell therapies in the setting of hematopoietic stem cell transplantation and hematologic malignancies under the guidance of the Czechowicz and Mackall Labs. Outside the lab, I enjoy making music, improving my photography, playing video games, and playing basketball and volleyball.



Joshua Guild

I graduated from UC Davis in 2014 with a B.S in Biochemistry and Molecular Biology, and came to Stanford as an M.D. student in 2017. Between undergrad and medical school, I spent 2 years in the lab of Sophie Dumont at UCSF studying the mechanics of cell division. I am now pursuing a Ph.D. in Tushar Desai's lab here at the Institute for Stem Cell Biology and Regenerative Medicine, and am studying the mechanisms and dynamics by which the alveolar epithelial barrier is restored following acute lung injury. I am originally from Santa Barbara, CA, and outside of lab you can find me driving up and down the coast looking for the perfect wave.

Stem Cell Biology and Regenerative Medicine Graduate Program

M.D./Ph.D. Class of 2020 – 2021



Daniel D. Liu

I graduated from Princeton University in 2018 with a degree in molecular biology and minors in computer science, quantitative and computational biology, and global health and health policy. My undergraduate research, conducted under Dr. Yibin Kang, focused on cancer stem cell biology and the molecular dynamics of metastasis. I am currently an MD-PhD candidate in the lab of Dr. Irv Weissman, where I study human neural stem cells in development, homeostasis, and disease. Outside of research, I enjoy combining my interests in art and science through painting.



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