INSIDE STANFORD MEDICINE

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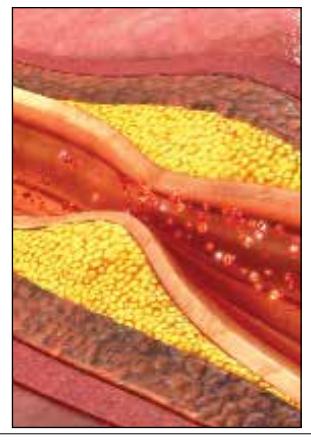

A new study describes how certain cells shift their identify to serve a protective role in people with atherosclerosis.

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Neuron-stimulated mice see what isn't there

By Bruce Goldman

Hallucinations are spooky and, fortunately, fairly rare. But, a new study suggests, the real question isn't so much why some people occasionally experience them. It's why all of us aren't hallucinating all the time.

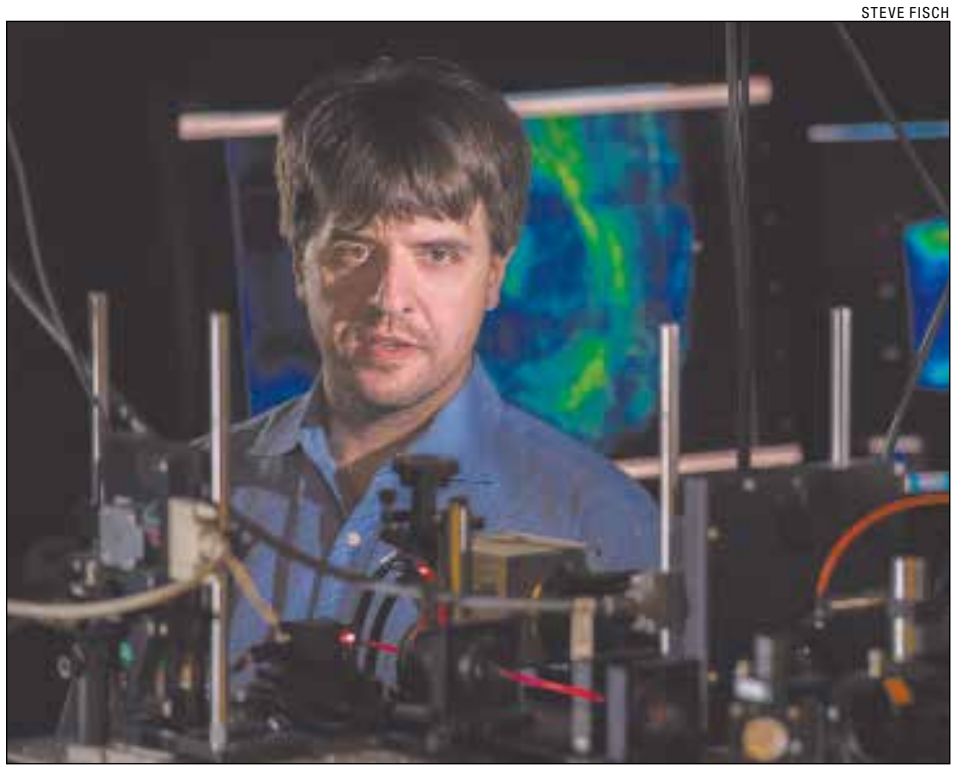
In the study, School of Medicine neuroscientists stimulated nerve cells in the visual cortex of mice to induce illusory images in the animals' minds. The scientists needed to stimulate a surprisingly small number of nerve cells, or neurons, in order to generate the perception, which caused the mice to behave in a particular way.

"Back in 2012, we had described the ability to control the activity of individually selected neurons in an awake, alert animal," said Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences. "Now, for the first time, we've been able to advance this capability to control multiple individually specified cells at once, and make an animal perceive something specific that in fact is not really there — and behave accordingly."

The study, published online July 18 in *Science*, holds implications for obtaining a better understanding of natural information processing in the brain, as well as psychiatric disorders such as schizophrenia, and points to the possibility of designing neural prosthetic devices with single-cell resolution.

Deisseroth is the study's senior author. Lead authorship is shared by staff scientists James Marshel, PhD, and Sean Quirin, PhD; graduate student Yoon Seok Kim; and postdoctoral scholar Timothy Machado, PhD.

STEVE FISCH



Karl Deisseroth is the senior author of a study describing how he and his colleagues stimulated nerve cells in the visual cortex of lab mice to induce illusory images in the animals' minds.

Using optogenetics

Deisseroth, who is a Howard Hughes Medical Institute investigator and holds the D. H. Chen Professorship, pioneered optogenetics, a technology enabling researchers to stimulate particular neurons in freely moving animals with pulses of light, and to observe the resulting effects on the animals' brain function and behavior.

In the new study, Deisseroth and his colleagues inserted a combination of two genes into large numbers of neurons in the visual cortex of lab mice. One gene encoded a light-sensitive protein that caused the neuron to fire in response to a pulse of laser light of a narrowly defined color — in this case, in the infrared spectrum. The other gene encoded a fluorescent protein that glowed green whenever the neuron was active.

The scientists created cranial windows in the mice by removing a portion of the animals' skulls to expose part of the visual cortex, which in both mice and humans is responsible for processing information relayed from the retina. The investigators protected this exposed area with a clear glass covering. They could then use a device they developed for the purpose of the study to project holograms — three-dimensional configurations of targeted photons — onto, and into, the visual cortex. These photons would land at precise spots along specific neurons. The researchers could monitor the resulting activity of nearly all individual neurons in two distinct layers of the cerebral cortex spanning about 1 square millimeter and containing on the order of several thousand neurons.

With their heads fixed in a comfortable position, the mice were shown random series of horizontal and vertical bars displayed on a screen. The researchers observed and recorded which neurons in the exposed visual cortex were preferentially activated by one or the other orientation. From these results, the scientists were able to identify dispersed populations of individual neurons that were "tuned" to either the horizontal or vertical visual display.

They were then able to "play back" these recordings in the form of holograms that produced spots of infrared light on just neurons that were responsive to horizontal, or to vertical, bars. The resulting downstream neuronal activity, even at locations relatively far from the stimulated neurons, was quite similar to that observed when the natural stimulus — a black horizontal or vertical bar on a white background — was displayed on the screen.

The scientists trained the mice to lick the end of a nearby tube for water when they saw See HALLUCINATIONS, page 6

Rheumatoid arthritis drug affords relief to patients who found little benefit from standard treatments

By Bruce Goldman

Rheumatoid arthritis patients getting little or no relief from conventional small-molecule drugs and injectable biologic drugs saw substantial improvement in their condition from daily use of an experimental compound in a large 24-week study led by a School of Medicine investigator.

A paper describing the results of the double-blind, randomized phase-3 clinical trial was published July 23 in *JAMA*.

"For patients who haven't See ARTHRITIS, page 7

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Drug combination heralds major shift in chronic lymphocytic leukemia treatment

By Krista Conger

A combination of two drugs keeps patients with chronic lymphocytic leukemia disease-free and alive longer than the current standard of care, according to a phase-3 clinical trial of more than 500 participants conducted at the School of Medicine and multiple other institutions.

The results of the trial are likely to change how most people with the common blood cancer are treated in the future, the researchers believe.

"I saw a marked improvement in my symptoms within two weeks of starting treatment, with little or no side effects," said trial participant Dan Rosenbaum, 57. "It's so unbelievable it is almost hard to talk about."

"These results will fully usher the treatment of chronic lymphocytic leukemia into a new era," said Tait Shanafelt, MD, professor of medicine at Stanford. "We've found that this combination of targeted treatments is both more effective and less toxic than the previous standard of care for these patients. It seems likely that, in the future, most patients will be able to forego chemotherapy altogether."

Shanafelt, who is the Jeanie and Stew Ritchie Professor, is the lead author of the study, which was published Aug. 1 in *The New England Journal of Medicine*. The senior author is Martin Tallman, MD, chief of the leukemia service at Memorial Sloan Kettering Cancer Center.

COURTESY OF DAN ROSENBAUM

Dan Rosenbaum with Jessie, his labradoodle. Rosenbaum participated in a study to assess how a combination of two drugs affected chronic lymphocytic leukemia, a common blood cancer.

Currently, CLL patients who are fit enough to tolerate aggressive treatment are treated intravenously with a combination of three drugs, two of which — fludarabine and cyclophosphamide — kill both healthy and diseased cells by interfering with DNA replication, and another, rituximab, that specifically targets the B cells that run amok in the disease.

But fludarabine and cyclophosphamide can cause significant side effects, including severe blood complications and life- See LEUKEMIA, page 6

New 'don't eat me' signal may provide basis for cancer therapies

By Christopher Vaughan

Researchers at the School of Medicine have discovered a new signal that cancers seem to use to evade detection and destruction by the immune system.

The scientists have shown that blocking this signal in mice implanted with human cancers allows immune cells to attack the cancers. Blocking other "don't eat me" signals has become the basis for other possible anti-cancer therapies.

Normally, immune cells called macrophages will detect cancer cells, then engulf and devour them. In recent years, researchers have discovered that proteins on the cell surface can tell macrophages not to eat and destroy them. This can be useful to help normal cells keep the immune system from attacking them, but cancer cells use these "don't eat me" signals to hide from the immune system.

The researchers had previously shown that the proteins PD-L1, CD47 and the beta-2-microglobulin subunit of the major histocompatibility class 1 complex, are all used by cancer cells to protect themselves from immune cells. Antibodies that block CD47 are in clinical trials. Cancer treatments that target PD-L1 or the PDL1 receptor are being used in the clinic.

The Stanford researchers now report they have found that a protein called CD24 also acts as a "don't eat me" signal and is used by cancer cells to protect themselves. A paper describing the research was published July 31 in *Nature*. Amira Barkal, an MD-PhD student, is the lead author. Irving Weissman, MD, professor of pathology and of developmental biology and director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and director of the Ludwig Center for Cancer Stem Cell Research, is the senior author.

NORBERT VON DER GROEBEN

Irving Weissman is the senior author of a paper about a previously unknown "don't eat me" signal on cancer cells. Blocking the signal may make cancer cells vulnerable to attack by the immune system.

"Finding that not all patients responded to anti-CD47 antibodies helped fuel our research at Stanford to test whether non-responder cells and patients might have alternative 'don't eat me' signals," said Weissman, who holds the Virginia and D.K. Ludwig Professorship for Clinical Investigation in Cancer Research.

Looking for additional signals

The scientists began by looking for proteins that were produced more highly in cancers than in the tissues from which the cancers arose. "You know that if cancers are growing in the presence of macrophages, they must be making some signal that keeps those cells from attacking the cancer," Barkal said. "You want to find those signals so you can disrupt them and unleash the full potential of the immune system to fight the cancer."

The search showed that many cancers produce an abundance of CD24 compared with normal cells and surrounding tissues. In further studies, the scientists showed that the macrophage cells that infiltrate the tumor can sense the CD24 signal through a receptor called SIGLEC-10. They also showed that if they mixed cancer cells from patients with macrophages in a dish, and then blocked the interaction between CD24 and SIGLEC-10, the macrophages would start gorging on cancer cells like they were at an all-you-can-eat buffet. "When we imaged the macrophages after treating the cancers with CD24 blockade, we could see that some of them were just stuffed with cancer cells," Barkal said.

Lastly, they implanted human breast cancer cells in mice. When CD24 signaling was blocked, the mice's scavenger macrophages of the immune system attacked the cancer.

CD47 complement?

Of particular interest was the discovery that ovarian and triple-negative breast cancer, both of which are very hard to treat, were highly affected by blocking the CD24 signaling. "This may be a vulnerability for those very dangerous cancers," Barkal said.

The other interesting discovery was that CD24 signaling often seems to operate in a complementary way to CD47 signaling. Some cancers, like blood cancers, seem to be highly susceptible to CD47-signaling blockage, but not to CD24-signaling blockage, whereas in other cancers, like ovarian cancer, the opposite is true. This raises the hope that most cancers will be susceptible to attack by blocking one of these signals, and that cancers may be even more vulnerable when more than one "don't eat me" signal is blocked.

"There are probably many major and minor 'don't eat me' signals, and CD24 seems to be one of the major ones," Barkal said.

The researchers now hope that therapies to block CD24 signaling will follow in the footsteps of anti-CD47 therapies, being tested first for safety in preclinical trials, followed by safety and efficacy clinical trials in humans.

For Weissman, the discovery of a second major "don't eat me" signal validates a scientific approach that combines basic and clinical research. "These features of CD47 and CD24 were discovered by graduate students in MD-PhD programs at Stanford along with other fellows," Weissman said. "These started as fundamental basic discoveries, but the connection to cancers and their escape from scavenger macrophages led the team to pursue preclinical tests of their potential. This shows that combining investigation and medical training can accelerate potential lifesaving discoveries."

Weissman is a member of Stanford Bio-X, the Stanford Cardiovascular Institute and the Stanford Cancer Institute.

Other Stanford researchers involved in the study were laboratory technician Rachel Brewer; graduate students Maxim Markovic and Mark Kowarsky; postdoctoral scholars Balyn Zaro, PhD, and Jason Hatakeyam, PhD; Layla Barkal, MD, PhD, resident physician in internal medicine; Venkatesh Krishnan, PhD, instructor of obstetrics and gynecology; and Oliver Dorigo, MD, PhD, associate professor of obstetrics and gynecology;.

The research was supported by the Virginia and D.K. Ludwig Fund for Cancer Research; the Stanford Medical Scientist Training Program; the National Cancer Institute; the National Heart, Lung and Blood Institute; anonymous donors; the Siebel Stem Cell Institute; and the California Institute for Regenerative Medicine.

Weissman is a co-founder, director and consultant at Forty Seven Inc., which holds licenses for CD47-based discoveries, partly tested in this manuscript.

Stanford's departments of Pathology and of Developmental Biology also supported the work. ISM

Stanford Health Care, Sutter sign letter of intent to explore oncology service

Stanford Health Care and Sutter Health have signed a letter of intent to formalize discussions focused on opportunities to jointly provide cancer care for patients and their families in the East Bay.

Initial activities between the two entities will focus on ways to build upon current and developing cancer-related services and care settings already in place within the two organizations' respective networks, to explore ways to increase access to cancer clinical trials and to make other enhancements to choice and quality of care for East Bay patients and their families.

Discussions also include potential plans to develop an integrated, multidisciplinary cancer center in the East Bay, modeled on the highly successful Stanford Cancer Center South Bay concept. This outpatient cancer center would serve as a local hub for cancer care and offer East Bay patients and their families access to the most advanced, complete and coordinated care from screening through survivorship.

"With this new collaboration, Stanford Health Care aims to bring the full complement of its world-class cancer prevention, treatment and clinical research programs to serve patients in the East Bay," said David Entwistle, president and CEO of Stanford Health Care. "Partnering with Sutter Health, with its well-established, high-quality cancer program in the area, is the ideal opportunity, and we are pleased to move forward with them in this effort."

"As an integrated network, Sutter Health has proudly provided accessible, high-quality care to our patients across the East Bay for over a century, and we're excited to build on this legacy," said Sarah Krevans, president and CEO of Sutter Health. "This announcement is an example of Sutter and Stanford's shared commitment as not-for-profit health systems to provide quality, compassionate and convenient care, and to do so in a way that delivers the best outcomes for our patients and our community."

> "A collaboration between Sutter and Stanford is a natural fit."

Julie Petrini, president of Bay Area Sutter Hospitals, agreed: "A collaboration between Sutter and Stanford is a natural fit, and one that will establish an unprecedented and easily accessible suite of services for all East Bay cancer patients. We are excited to formalize our discussions with Stanford through this LOI."

Complete cancer care, locally

The intent of the collaboration is to increase access to high-quality cancer care for patients as close to home as possible by building on the strength of Stanford's leadership in cancer care and clinical research, the Stanford Medicine network and Sutter's integrated network. Both entities have a deep commitment to caring for the whole patient, and together their efforts will surround patients and their families with a full spectrum of coordinated, supportive care. The new East Bay oncology collaboration would help local patients simplify care coordination, reduce travel time and focus on treatment and recovery.

Innovative treatments

The treatment of cancer is a rapidly evolving field. A collaboration between Stanford and Sutter Health would greatly improve access for **See ONCOLOGY, page 3**

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STANFORD MEDICINE

Possible drug target for deadly heart condition identified

By Jonathan Wosen

A genetic mutation linked to dilated cardiomyopathy, a dangerous enlargement of the heart's main pumping chamber, activates a biological pathway normally turned off in healthy adult hearts, according to a study by researchers at the School of Medicine.

Chemically inhibiting the pathway corrected the mutation's effects in patient-derived heart cells in a lab dish, the study found. The researchers accomplished this with drugs already approved by the Food and Drug Administration.

The findings, which were published online July 17 in *Nature*, suggest that existing drugs could one day be repurposed to treat dilated cardiomyopathy. More broadly, the study demonstrates how patient-derived heart cells can help scientists better study the heart and screen new candidate drugs.

"With 10 milliliters of blood, we can make clinically usable amounts of your beating heart cells in a dish," said the study's senior author, Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute and a pioneer of the technique. "And if you tell me you're taking some kind of medication for your heart — like beta-blockers or statins — we can add that to see how it affects your heart. That's the beauty of this approach."

The study's other senior author is Ioannis Karakikes, PhD, assistant professor of cardiothoracic surgery at Stanford. Lead authorship is shared by former Stanford postdoctoral scholar Jaecheol Lee, PhD; Stanford medical fellow Vittavat Termglinchan, MD; and Sebastian Diecke, PhD, a researcher at the Max Delbrück Center in Berlin.

The researchers studied heart muscle cells grown from patients with a genetic mutation associated with dilated cardiomyopathy. Heart cells with a mutation in lamin, which forms part of the nuclear envelope, failed to beat properly — just like in patients with the disease. The scientists found that the defect was the result of a surge in the platelet-derived growth factor pathway. This pathway is important in the formation of blood vessels and normally only activates when the heart first forms or is under stress. Treating heart cells with existing drug inhibitors of the pathway restored regular, rhythmic beating.

> The work is an example of Stanford Medicine's focus on precision health.

Don't stop the beat

In dilated cardiomyopathy, the heart's main pumping chamber, the left ventricle, expands so much that the heart can no longer beat regularly. Patients experience shortness of breath, chest pain and, in severe cases, sudden and deadly cardiac arrest. Approximately 1 in every 250 Americans suffer from a form of dilated cardiomyopathy of which the exact cause is not known, though 20% to 35% of these cases run in families. Doctors at Stanford Health Care's heart failure and cardiomyopathy clinic treat many patients with this condition.

Previous studies correlated mutations in lamin to familial dilated cardiomyopathy, but it seemed like an odd connection. Lamin forms part of the nuclear envelope, a structure that separates DNA from the rest of the cell and regulates the movement of molecules in and out of the nucleus — not exactly an obvious candidate for regulating heart function.

"We were puzzled," said Wu, the Simon H. Stertzer, MD, Professor and professor of medicine and of radiology. "Why would a mutation in a nuclear envelope protein not involved in squeezing of the heart, such as sarcomere protein, or in electrophysiology of the heart, such as an ion channel, lead to dilated cardiomyopathy?"

To solve the mystery, the researchers needed to study the lamin mutation in heart muscle cells. Excising a tissue sample from a patient's heart, an invasive medical procedure, was not a good option. Mouse tissue was another possibility, but mouse findings don't always hold up in humans.

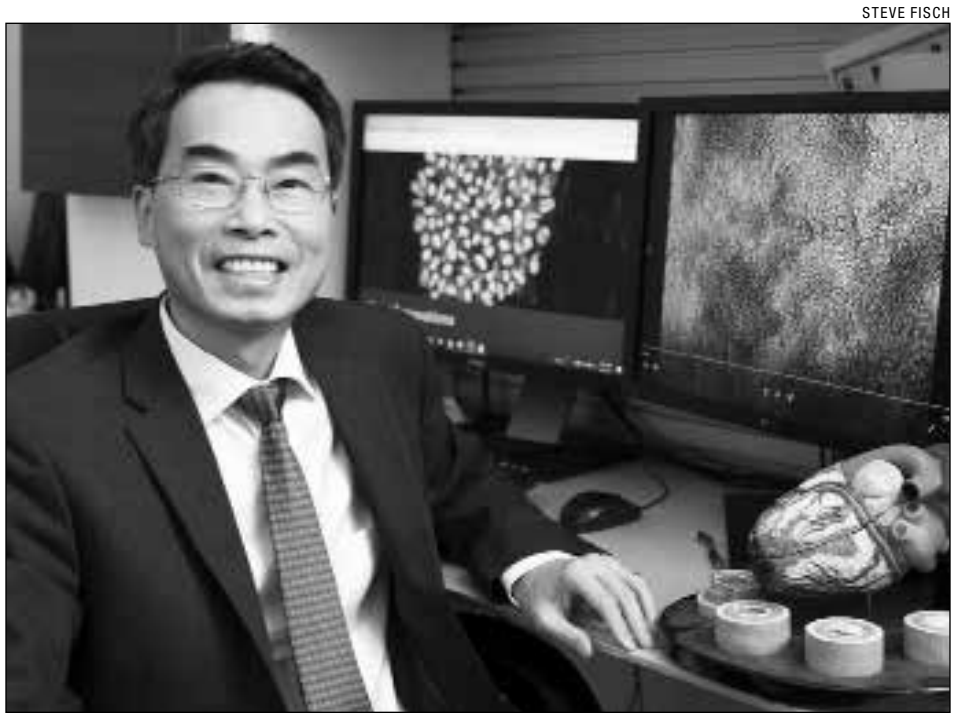
Instead, the scientists generated heart cells by turning back the clock on patient-derived skin cells to make induced pluripotent stem cells, which can become any of the specialized cells found throughout the body. While the researchers used skin cells in the study, Wu said that the same technique can also be done with 10 milliliters of blood — roughly two teaspoons.

Heart muscle cells grown in a dish pulse rhythmically, just as they do in the body. But cells from members of a family with lamin mutations and a history of dilated cardiomyopathy beat noticeably off-rhythm and had irregular electrical activity. The defect could be fixed by swapping in a normal copy of the gene with a gene-editing technology. Introducing the mutation into cells from healthy patients caused those cells to beat off-rhythm too. Cells with the lamin mutation had abnormal levels of calcium, a key ion that regulates muscle contractions.

Getting back on rhythm

As part of the nuclear envelope, lamin interacts with a tightly packed form of DNA known as heterochromatin. Interestingly, the researchers found by various DNA sequencing techniques that cells with the lamin mutation had fewer regions of heterochromatin. Since DNA packing affects what genes get activated or shut off, the researchers looked at gene-activation patterns to see which pathways went awry in cells with the mutation — and what they could do about it.

STEVE FISCH



Joseph Wu is the co-senior author of a study that has uncovered how a genetic mutation contributes to familial dilated cardiomyopathy. Existing drugs corrected the defect in heart cells grown in a petri dish.

"Although we did all this sequencing and other experiments, without a specific target, we cannot provide the right therapy," Lee said.

They found nearly 250 genes that were more highly activated in mutated cells than in normal cells. Many of the genes were part of the platelet-derived growth factor, or PDGF, pathway. When the researchers tested heart tissue from dilated cardiomyopathy patients with a lamin mutation, they saw signs that the same pathway was activated.

But did activation of the PDGF pathway cause abnormal rhythms or the other way around? To test this, the researchers treated heart cells with two drugs, crenolanib and sunitinib, that inhibit a key PDGF receptor. After treatment, heart cells with the lamin mutation began beating more regularly, and their gene-activation patterns more closely matched those of cells from healthy donors.

These two drugs are FDA-approved for treating various cancers. But previous work from Wu's team shows that the drugs may damage the heart at high doses, which will make finding the right dose or a safer alternative critical.

The current study is part of a broader effort by the researchers to use these patient-derived cells in a dish to screen for and discover new drugs. It's why the Wu lab has generated heart muscle cells from more than 1,000 people, including Wu, his son and daughter.

"Our postdocs have taken my blood and differentiated my pluripotent stem cells into my brain cells, heart cells and liver cells," Wu said. "I'm asking them to test some of the medications that I might need to take in the future."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

In addition to serving as director of the Stanford Cardiovascular Institute, Wu is a member of Stanford Bio-X, Stanford ChEM-H, the Stanford Cancer Institute and the Stanford Maternal & Child Health Research Institute.

Other Stanford co-authors of the study are postdoctoral scholars Ilanit Itzhaki, PhD, Joe Zhang, MD, PhD, Xingqi Chen, PhD, and Isaac Perea Gil, PhD; instructors Chi Keung Lam, PhD, Edward Lau, PhD, and Haodi Wu, PhD; former postdoctoral scholars Priyanka Garg, PhD, Timon Seeger, MD, and Jared Churko, PhD; graduate student Mohamed Ameen; Karim Sallam, MD, clinical assistant professor of medicine; clinical instructor June-Wha Rhee, MD; research assistant Tony Chour; former research assistants Rinkal Chaudhary and Matthew Greenhaw; Paul Wang, MD, professor of medicine; Michael Snyder, PhD, professor and chair of genetics; and Howard Chang, MD, PhD, professor of dermatology.

This study was supported by the American Heart Association, the National Institutes of Health, the California Institute for Regenerative Medicine, the Leducq Foundation, the Prince Mahidol Award Foundation, the German Research Foundation, the National Research Foundation of Korea and the Howard Hughes Medical Institute. ISM

Oncology

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East Bay cancer patients to new opportunities for clinical care and clinical research, including an expanded array of clinical trials.

"Working with Sutter Health in the East Bay will broaden opportunities for participation in some of the world's most innovative cancer treatment trials," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "With breakthroughs in the detection, prevention and treatment of cancer and its side effects, Stanford Medicine's physician-scientists are actively investigating new therapies and working to make sure that they are available to everyone who needs them. This collaboration presents a real opportunity for improvement for patients, and a benefit to the progress of cancer science, as more inclusion enables more discoveries."

Stanford Health Care and Sutter Health also expect that this opportunity will greatly enhance their shared commitment to health equity by improving access to exceptional care for underrepresented minorities in the community who often lack access to advanced care options and the ability to participate in clinical trials.

Efficient, high-quality care

To this collaboration, Stanford Health Care brings its strength as a National Cancer Institute-designated Comprehensive Cancer Center, and its leadership as one of the founding members of the National Comprehensive Cancer Network, an alliance of 26 of the world's leading cancer centers dedicated to improving the quality and effectiveness of care provided to patients with cancer.

Stanford Health Care is consistently recognized as one of the top hospitals in America for cancer care by *U.S. News & World Report*, recognized for overall quality and safety by Vizient in 2018 and awarded an 'A' from The Leapfrog Group's spring 2019 Leapfrog Hospital Safety Grade.

A collaboration with Stanford and Sutter Health would also build on the efficient and high quality of care for which Sutter Health's integrated network is consistently recognized, and would provide East Bay residents with seamless coordination of cancer care and support services from one caregiver to another.

Four hospitals within Sutter Health, including Alta Bates Summit Medical Center, have been recognized as top hospitals in California by *U.S. News & World Report*. ABSMC has also received the highest rating (5 stars) from the Centers for Medicare & Medicaid Services Hospital Quality Ratings. Additionally, Sutter Health includes many of California's top-performing, highest quality physician organizations. ISM

A key gene behind hallmark of Lou Gehrig's disease identified

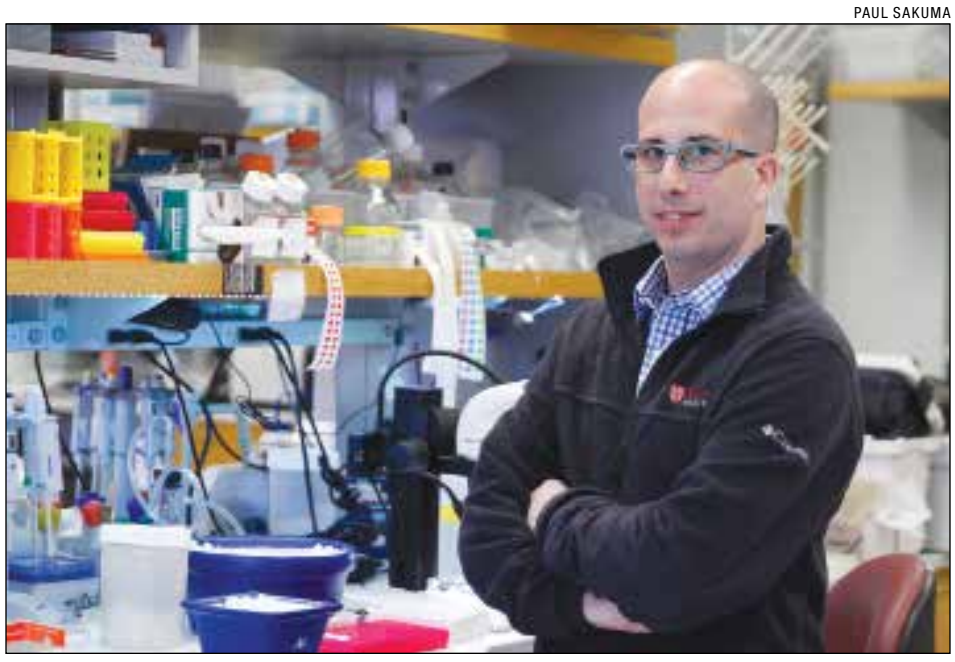
By Hanae Armitage

Inside the brains of patients with amyotrophic lateral sclerosis, a debilitating neurodegenerative disease, is a telltale sign that marks almost every case: clumps of toxic proteins.

Now, researchers from the School of Medicine and their collaborators have pinpointed a key gene behind the formation of one type of these neuron-damaging aggregates. They've also shown how inhibiting the gene's function curbs production of the harmful protein.

"We know that these protein-rich aggregates are a clear hallmark of ALS," said Aaron Gitler, PhD, professor of genetics. "But this finding allows us a deeper look into how those aggregates are made, and potentially how we can hinder that process."

PAUL SAKUMA



Aaron Gitler is the senior author of a paper that identifies a gene crucial to the formation of toxic proteins in amyotrophic lateral sclerosis and that shows how it could inform potential therapies for the disease.

The gene, RPS25, codes for a piece of cellular machinery necessary for creating the protein-based gunk that amasses in some forms of ALS and damages healthy neurons. When the gene's activity was experimentally depleted — in yeast, in neurons derived from patients with ALS and in fruit flies — Gitler and his team saw levels of the lethal protein drop by about 50 percent across the board.

The team also tested the function of RPS25 in human cells modeling Huntington's disease and spinocerebellar ataxia, two other neurodegenerative illnesses that have protein-aggregate "hallmarks" similar to ALS, said Shizuka Yamada, a graduate student in Gitler's lab. There, too, inhibiting the gene helped tamp down the levels of bad protein.

It's still early days, Yamada said, but hampering the RPS25 gene seems like a promising target for reducing the destructive proteins seen in ALS and even extending life span, as was seen in the fruit fly model of ALS with low activity levels of the gene.

A paper detailing the results of the research was published July 29 in *Nature Neuroscience*. Gitler, who holds the Stanford Medicine Basic Science Professorship, is the senior author. Yamada is the lead author.

Also known as Lou Gehrig's disease, ALS is a condition that kills off motor neurons, which are crucial to all physical tasks, from brushing one's hair to breathing. The root cause behind every case is not always the same; there's a slew of genetic factors that play into the onset of ALS. Yet one gene is often the culprit. In ALS, it harbors a string of DNA that erroneously repeats itself.

It's these DNA repeats that are transformed into the harmful proteins that build up in the brain. As the proteins amass, they interfere with healthy neurons, blocking the cells' ability to function normally.

Not made like other proteins

Outside of their toxic properties, what's notable about the protein aggregates is that they aren't made like other proteins found in the body, Yamada said. "These repeats actually shouldn't be made into proteins at all," she said. "They come from DNA that isn't supposed to code for anything, and yet somehow the proteins come to be anyway."

During run-of-the-mill protein formation, the ribosome, a sort of molecular machine that resides in the cell, processes messenger RNA, which contains genetic code based on DNA, and turns it into the raw materials of a protein. That process is called translation, and it's initiated by a code in the mRNA that shows the ribosome where to start translating. The ALS-associated DNA repeats don't have that start code, unlike normal mRNA.

"So regular translation doesn't work with the repeats," Yamada said. But it turns out there's a molecular workaround: an unconventional translation process called repeat-associated non-AUG translation, or RAN translation, that turns the ALS repeats into destructive protein bodies.

Putting the brakes on RPS25

The exact mechanism of RAN translation and its role in human biology is not clear, but scientists do know that it still depends on the ribosome. To better understand the process, Gitler and Yamada turned to yeast, a simple organism that still has the major proteins and pathways of human cells. One at a time, the researchers decreased the function of individual yeast genes and monitored the fungus' RAN function. When subdued, several genes swayed RAN function, but one in particular, RPS25, stood out. With the gene hindered, production of the toxic protein fell by 50 percent.

The researchers also saw a 50 percent dip in the toxic protein when they tested how neurons derived from patients with ALS fared without RPS25.

"We were really excited to see the decrease in repeat proteins carry over into human cells," Yamada said. "It's always pretty cool when yeast biology can directly inform human biology." Because these cells came from patients who suffer from ALS, the research offered a reliable glimpse into how the neurons of individuals with ALS would respond to lower levels of RPS25, she said.

"Through genomic analyses, we could see that the ALS-associated repeats were still there; the sequences hadn't changed," Yamada said. "What was changing was the output of the ribosome; the repeats weren't being made into toxic proteins nearly as often."

Slashing a part of the cell's protein-making machine might sound risky, but it turns out a defunct RPS25 gene doesn't spoil normal protein production. Yet the researchers also showed that an inactive RPS25 gene affects more than just the ALS repeats; the dysfunctional gene similarly stunted erroneous protein production in cellular models of Huntington's disease and spinocerebellar ataxia, two neurodegenerative illnesses that have hallmark protein aggregates similar to ALS.

Moving toward more complexity

Finally, the researchers turned to fruit fly models of ALS to investigate how depleting RPS25 affected the insect overall. Not only did they see a similar decrease in toxic protein levels, they also saw an increased life span in the flies that lacked fully functional RPS25. Flies that harbored both the ALS mutation and a working RPS25 gene died by day 29, on average, while those that had the ALS mutation and lower amounts of RPS25 lived on average for 38 days. A healthy fruit fly lives about 50 days on average.

The findings are intriguing, Yamada said, but before the scientists can begin to pursue RPS25 as a drug target, the team has a couple boxes to tick off. The team now is investigating how a more complex animal model — like a mouse — would fair without RPS25.

"With the fruit flies, we tampered with the gene; we didn't remove it completely," Yamada said. "Whether an animal can survive without the gene entirely is a big part of our next step."

Furthermore, Yamada said, she and Gitler are still after a clearer picture of RAN translation in humans, overall. "Does it only occur under neurogenerative conditions? Or is there a broader role for it in healthy individuals?" she said. "We don't know the answer to those questions yet, and it will be crucial to figure out before pursuing RPS25 as a therapeutic target."

Other Stanford co-authors of the study are graduate students Naomi Genuth and Nicholas Kramer; postdoctoral scholar Rosslyn Grosely, PhD; research technician Lisa Nakayama; high school student Shirleen Fang; research assistant Tai Dinger; Maria Barna, PhD, assistant professor of genetics and of developmental biology; and Joseph Puglisi, PhD, professor of structural biology.

Researchers from the Mayo Clinic, the University College London and the University of Southern California also contributed to the research. **ISM**

School readiness impaired in preschoolers with ADHD symptoms

By Erin Digitale

Preschoolers with symptoms of attention-deficit hyperactivity disorder are much less likely than other children their age to be ready for school, new research from the School of Medicine has found.

The study, which was published online July 21 in *Pediatrics*, is among the first to comprehensively examine school readiness in young children with ADHD. Several previous studies have addressed academic difficulties in school-aged children with ADHD, but few studies have investigated whether these children start school behind their peers.

"We were pretty surprised at the proportion of kids within the ADHD group who were not school-ready," said the study's senior author, Irene Loe, MD, assistant professor of pediatrics. Seventy-nine percent of children with ADHD had impaired school readiness compared with 13 percent of children in a control group, the study found. "It's a really high number," Loe said.

The study's lead author is Hannah Perrin, MD, who was a fellow in developmental and behavioral pediatrics at Stanford when the research was done.

The main symptoms of ADHD — inattention, hyperactivity and impulsivity — can be normal in toddlers, and these behaviors sometimes persist into the preschool years even in children who will not ultimately meet the diagnostic criteria for ADHD. This makes the disorder difficult to diagnose in preschoolers. "A lot of these kids are not identified until they're really having a lot of trouble in the school setting," Loe said.

The study included 93 children, all of whom were 4 or 5 years old. Nearly all had attended or were currently enrolled in preschool, and some were enrolled in kindergarten. The ADHD group included 45 children who previously had been diagnosed with the disorder or were identified by their parents as having significant levels of ADHD symptoms. The comparison group consisted of 48 children without ADHD. The researchers tested all the children to confirm their levels of ADHD symptoms.

The researchers conducted tests and administered parent questionnaires to measure five areas of the children's functioning: physical well-being and motor development; social and emotional development; approaches to learning; language development; and cognition and general knowledge. "Approaches to learning" included measures of executive function, which is a person's ability to prioritize actions and tasks and exercise self-control to regulate behavior and meet long-term goals.

SUZANNE TUCKER/SHUTTERSTOCK.COM

Children were considered impaired in an area of functioning if their assessment

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Identity-shifting cells protect against rupture in atherosclerosis

SCIENCEPICS/SHUTTERSTOCK.COM

Atherosclerosis occurs when arteries get clogged by plaque, a buildup of fats, cholesterol and molecular particulate. Plaque grows within the layers of tissue that form the artery, narrowing the blood conduit.

By Hanae Armitage

Changing your identity to protect others might sound like something reserved for comic book vigilantes, but a study led by researchers at the School of Medicine has found a select group of cells in artery walls do just that.

For these cells, the identity shift happens in a disease called atherosclerosis, which occurs when arteries get clogged by plaque, a buildup of fats, cholesterol and molecular particulate.

"We know that things like poor diet and lack of exercise contribute to atherosclerosis," said Thomas Quertermous, MD, professor of cardiovascular medicine at Stanford. "But molecularly speaking, researchers still don't know how the disease progresses or, conversely, is hindered." This new work, he said, takes a big step toward addressing that question.

Plaque grows within the layers of tissue that form the artery, as opposed to inside the tube itself, causing the blood conduit to narrow. Too much plaque tears open the tissue, allowing the built-up gunk to flood the interior of the tube. That leads to a clot, which can cause artery blockage and often a heart attack.

In people with atherosclerosis, cells that make up the artery wall transform and invade the area containing the plaque, or lesion, and form something called a fibrous cap, which acts kind of like a lid to prevent the plaque from bursting into the artery. Now, Quertermous and his colleagues have characterized the identity of these transformed cells, giving key insights into something called plaque stability, which determines the likelihood of a plaque bursting. The more robust the fibrous cap, the more stable the plaque and the less likely it is to rupture.

Thomas Quertermous

The team has also pinpointed a gene that seems to be behind the cells' transformation. What's more, when they looked at populationwide genomic data, they saw that individuals who had more activity in this particular gene were at a decreased risk for heart attack.

"Logically, it makes sense — the more cells that help form the fibrous cap, the stronger the protection against plaque rupture and therefore the less risk of a heart attack," said Quertermous, who is the William G. Irwin Professor in Cardiovascular Medicine.

A paper describing the details of the study was published July 29 in *Nature Medicine*. Quertermous shares lead authorship with Juyong Kim, MD, instructor of medicine. The lead author is Robert Wirka, MD, instructor of cardiovascular medicine.

Under healthy conditions, the smooth muscle cells that make up the wall of arteries control the vessel's dilation, expanding and contracting to regulate blood flow and blood pressure. But when plaque in the artery starts to build, smooth muscle cells begin to shift.

'Kind of like a scab'

The cells actually move toward the plaque lesion, Wirka said. The genes that make the smooth muscle cells begin to shut off and, in their place, new genes turn on. Then, like Clark Kent to Superman, the smooth muscle cells ditch their everyday identity for a heroic version of themselves — the fibromyocyte, similar to a fibroblast, a cell type known for its role in connective tissue and collagen production. The fibromyocytes then form a protective cap over the cholesterol, fat and molecular debris that compose arterial plaque.vv

"It's kind of like a scab over a wound," Quertermous said. "Only in this case, the scab also keeps the plaque stable."

Researchers have known that smooth muscle cells reinvent themselves during atherosclerosis, but it wasn't clear exactly what their new identity was. Scientists thought these cells could have a beneficial role, but also suspected they could transform into dysfunctional immune cells that promote inflammation and worsen the condition.

To figure out the smooth muscle cells' intentions, Wirka, Quertermous and their colleagues used an experimental technique in mice called lineage tracing, which allowed the scientists to track the whereabouts of specific cells and cells derived from those cells. The group labeled arterial smooth muscle cells in the mice with a special chemical that turns the cells red under a microscope. Then, after inducing a mouse version of atherosclerosis, they checked the arteries for signs of smooth muscle cell movement. They observed that some of the red-labeled smooth muscle cells had moved into the plaque from their original homes in the artery.

New place, new name

Wirka and Quertermous then profiled all the cells in the artery, analyzed the collection of cells — immune, smooth muscle, fibromyocyte and more — and ran gene expression analyses to see which genes were "on" in each individual cell. According to the gene expression analysis, the red-labeled smooth muscle cells that migrated to the plaque were sporting a new look.

"These cells exhibited a sort of swap: Patterns of gene activity that track with smooth muscle cells decreased, and activity of genes that give rise to fibromyocytes increased," Quertermous said. "The data allowed us to, beyond a shadow of a doubt, characterize these particular cells in the plaque as smooth muscle cells that have turned into fibromyocytes." Remarkably, Wirka said, the researchers found no evidence that smooth muscle cells transformed into plaque-destabilizing immune cells, resolving a long-standing question in the field.

Next, Quertermous and Wirka used a form of computer modeling to bridge mouse biology to humans. They took tissue samples from human patients with atherosclerosis who'd received heart transplants. The scientists analyzed cells from the human arteries with the same single-cell gene expression method used in the mouse tissue.

With data from both human and mouse atherosclerotic tissue, the computer model accurately identified cell types, regardless of species. Importantly, the researchers found the same phenomenon occurring in the human arteries: Smooth muscle cells were also transforming into fibromyocytes during human disease.

The gene behind the transition

Quertermous and Wirka went even one step further, identifying the gene that seems to drive the transition from smooth muscle cell to fibromyocyte during atherosclerosis. In Quertermous' earlier work, he identified one particular gene, TCF21, that was associated with a person's risk for coronary artery disease.

"It's been my theory all along that TCF21 gets reactivated in the vessel wall and is a key contributor to this cell type transition," Quertermous said.

So he tested that theory in a mouse model of atherosclerosis, disabling the TCF21 gene to see if it exacerbated the disease. He and Wirka saw that mice without TCF21 formed fewer fibromyocytes overall, fewer fibromyocyte cells in the plaque and a less-sturdy fibrous cap.

Quertermous and Wirka said that TCF21 could likely help guide them toward a new therapy for coronary artery disease. But before taking steps in that direction, there's still more to understand about TCF21 and how it mediates this transformation at the molecular level, they said. "Now we have good evidence that the ability for smooth muscle cells to undergo this transformation to fibromyocytes is important to protect against clinically significant coronary disease, but the timing and extent of this transformation is likely also important," Wirka said.

Other Stanford co-authors of the study are senior research scientist Dhananjay Wagh, PhD; postdoctoral scholars David Paik, PhD, Milos Pjanic, PhD, and Manabu Nagao, PhD; lab managers Trieu Nguyen and Robyn Fong; research scientist Ramendra Kundu, PhD; John Coller, PhD, director of the Stanford Functional Genomics Facility; research assistant Tiffany Koyano; Joseph Woo, MD, professor of cardiothoracic surgery; former graduate student Boxiang Liu, PhD; Stephen Montgomery, PhD, associate professor of pathology; Joseph Wu, MD, PhD, professor of cardiovascular medicine and of radiology.

Quertermous is a member of Stanford Bio-X, the Stanford Cardiovascular Institute and the Stanford Maternal & Child Health Research Institute.

Researchers from the University of Virginia, the University of Arizona and University of Hawaii also contributed to the work.

The research was funded by the National Institutes of Health. Stanford's Department of Medicine also supported the work. **ISM**

ADHD

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scores in that area were more than one standard deviation worse than the mean score for their age. They were considered unready for school if they were impaired in two or more of the five areas of functioning measured in the study.

Struggling in 4 of 5 areas

Children with ADHD were no more likely than their peers to show impairment in the area of cognition and general knowledge, the study found. This area includes IQ and, importantly, knowledge people traditionally associate with kindergarten readiness, such as being able to identify letters, numbers, shapes and colors.

But children with ADHD were much more likely than their peers to struggle in all four other areas measured. They were 73 times more likely than children without ADHD to be impaired in approaches to learning; more than seven times as likely to have impaired social and emotional development; six times as likely to have impaired language development; and three times as likely to have impaired physical well-being and motor development.

Irene Loe

The assessment was broader than other school-readiness measures researchers have used in the past, Loe said. "We looked at many aspects of the child more comprehensively," she said, adding that approaches to learning or executive function as a component of school readiness has been especially under-studied.

The findings suggest that identifying and helping preschoolers with significant levels of ADHD symptoms could reduce their struggles in elementary school.

"We need to help general pediatricians figure out how they can flag kids who might be at risk for school failure," Loe said. Families also need better access to behavioral therapy for preschoolers with ADHD, which is not always available or covered by insurance, even though it is recommended as the first-line ADHD treatment for this age group, she added.

"Thinking about how we can provide services for young children with ADHD or who are at high risk for the diagnosis is really important," she said.

Loe is a member of the Stanford Maternal & Child Health Research Institute. Nicole Heller, a former clinical research coordinator at Stanford, is also a co-author of the research.

The study was funded by the Maternal and Child Health Bureau, which is part of the U.S. Department of Health and Human Services; a Katharine McCormick Faculty Scholar Award; a Stanford Children's Health and Child Health Research Institute Pilot Early Career Award; and the National Institutes of Health.

Stanford's Department of Pediatrics also supported the work. **ISM**

Medical school awarded $53 million to improve translational medicine

By Kris Newby

The Stanford School of Medicine has received a five-year, $53 million grant renewal from the Clinical and Translational Science Award Program.

The CTSA Program is overseen by the National Center for Advancing Translational Sciences at the National Institutes of Health.

"This funding will help us strengthen our clinical and translational research infrastructure in a way that will prepare us for the remarkable transformation underway in precision health and population health research," said Mark Cullen, MD, senior associate vice provost for research at Stanford and senior associate dean for research at the School of Medicine. "Ultimately, this will accelerate the application of research discoveries into clinical care, helping people live longer, healthier lives."

With the grant renewal, Stanford will continue its collaborations with a national network of 50-plus academic medical research institutions, known as CTSA Program hubs. The hubs work together to share resources and improve the processes that turn research discoveries into medical treatments and cures.

The funding will build on the School of Medicine's efforts to:

- Educate the next generation of researchers with the skills required to conduct innovative clinical and translational research in health care delivery and wellness. Funding also supports team science through training and pilot projects that foster collaborations with professionals trained in different fields.
- Enhance community engagement to ensure that the outcomes of the research benefit all segments of the population, including people with rare diseases, minorities and women, and vulnerable populations, such as children and elderly people. A new recruitment program will expand the school's efforts to engage potential research participants in all of these populations.
- Strengthen the School of Medicine's Research Office to provide investigative teams with ready access to the resources and services necessary to efficiently translate discoveries into ways to improve the health and well-being of individuals and populations.
- Develop the data science methods, processes, services and assessment tools to help researchers find ways of improving health outcomes while reducing costs, promoting regulatory compliance and ensuring data accessibility.
- Share Stanford resources — such as expertise in artificial intelligence, bioinformatics and precision health — with the other CTSA Program hubs.

"Stanford Medicine is proud to be a part of the CTSA Program, and I'm delighted that our invaluable contributions have again been recognized with this new award," said Lloyd Minor, MD, dean of the School of Medicine. "The funding and collaborative network the CTSA Program has established will enable our physicians and scientists to more rapidly move breakthroughs from bench to bedside, to train the researchers of tomorrow and to deliver precision health to the world."

The NIH launched the CTSA Program in 2006 to incentivize research institutions to find creative ways to more rapidly move breakthroughs in basic research to patient care.

The university previously received CTSA Program grants in 2008 and 2013, with the latter grant totaling $45 million. In the decade since joining the CTSA Program, Stanford Medicine's major CTSA-related achievements include:

- The launch of the Stanford Predictives and Diagnostics Accelerator, a program that assists efforts to research, develop and deploy technologies for improving diagnoses and better predicting the progression of disease.
- A data science resource portal from which researchers can access advanced tools and data platforms and connect with experts in diverse methodologies for conducting biomedical research. It also provides researchers with access to almost 200 health-related data sets.
- Establishment of a biobank management system that is capable of reliably tracking biological samples collected in studies and linking each with associated health records and molecular data. This system enables researchers to gain collaborative access to unused biospecimens and related data for use in efforts to identify biomarkers.
- A series of research and regulatory compliance programs, including the expansion of a clinical research management system across the institution, a new ClinicalTrials.gov compliance process and more staff for ensuring improved research quality.
- Continued efforts to streamline the processes involved with translational research, from first-in-human clinical trials through implementation of preventive measures, treatments and diagnostics into communities.

Information about the NIH's National Center for Advancing Translational Sciences CTSA program can be found at http://www.ncats.nih.gov. For more information about Stanford's CTSA program, visit the Spectrum website at http://med.stanford.edu/spectrum.html. ISM

Hallucinations

continued from page 1

a vertical bar but not when they saw a horizontal one or saw neither. Over the course of several days, as the animals' ability to discriminate between horizontal and vertical bars improved, the scientists gradually reduced the black-white contrast to make the task progressively harder. They found that the mice's performance perked up if the scientists supplemented the visual displays with simultaneous optogenetic stimulation: For example, if an animal's performance deteriorated as a result of a lowered contrast, the investigators could boost its discrimination powers by stimulating neurons previously identified as preferentially disposed to fire in response to a horizontal or vertical bar.

This boost occurred only when the optogenetic stimulation was consistent with the visual stimulation — for example, a vertical bar display plus stimulation of neurons previously identified as likely to fire in response to vertically oriented bars.

Hallucinating mice

Once the mice had become adept at discriminating between horizontal and vertical bars, the scientists were able to induce tube-licking behavior in the mice simply by projecting the "vertical" holographic program onto the mice's visual cortex. But the mice wouldn't lick the tube if the "horizontal" program was projected instead.

"Not only is the animal doing the same thing, but the brain is, too," Deisseroth said. "So we know we're either recreating the natural perception or creating something a whole lot like it."

In their early experiments, the scientists had identified numerous neurons as being tuned to either a horizontal or a vertical orientation, but they hadn't yet directly stimulated those particular neurons optogenetically. Once the mice were trained, optogenetic stimulation of small numbers of these neurons was enough to get mice to respond with appropriate licking or nonlicking behavior.

The researchers were surprised to find that optogenetically stimulating about 20 neurons — or fewer in some cases — selected only for being responsive to the right orientation could produce the same neuronal activity and animal behavior that displaying the vertical or horizontal bar did.

"It's quite remarkable how few neurons you need to specifically stimulate in an animal to generate a perception," Deisseroth said.

"A mouse brain has millions of neurons; a human brain has many billions," he said. "If just 20 or so can create a perception, then why are we not hallucinating all the time, due to spurious random activity? Our study shows that the mammalian cortex is somehow poised to be responsive to an amazingly low number of cells without causing spurious perceptions in response to noise."

Deisseroth is a member of Stanford Bio-X and of the Wu Tsai Neurosciences Institute at Stanford.

Other Stanford co-authors of the study are graduate student Brandon Benson; postdoctoral scholars Jonathan Kadmon, PhD, Masatoshi Inoue, PhD, and Hideaki Kato, PhD; life science researcher Cephra Raja; lab managers Adelaida Chibukhchyan and Charu Ramakrishnan; and Surya Ganguli, PhD, assistant professor of applied physics.

Stanford's Office of Technology Licensing has filed a patent application for intellectual property associated with the work. ISM

Leukemia

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threatening infections that are difficult for many patients to tolerate.

Rituximab plus ibrutinib

The new drug combination pairs rituximab with another drug, ibrutinib, which also specifically targets B cells.

In the trial, 529 participants with newly diagnosed chronic lymphocytic leukemia were randomly assigned in a 2:1 ratio to receive either six courses of ibrutinib and rituximab, followed by ibrutinib until their disease progressed, or six courses of traditional chemotherapy consisting of the drugs fludarabine, cyclophosphamide and rituximab.

The researchers followed each of the participants, who were recruited at one of more than 180 study sites across the country, for nearly three years and logged the length of both their "progression-free survival," or the period during which their disease did not progress, and their overall survival.

Rosenbaum, a partner in a global strategy consulting firm and avid tennis player, was one of the participants randomly assigned to receive the experimental treatment. He noticed a difference in his symptoms almost immediately.

"I hadn't realized how fatigued I had become," he said of the weeks preceding his treatment. "I could barely play a single set of tennis, and I would be wiped out for days afterward. My lymph nodes were so swollen it was impossible to button the top button of my shirt collar. But within the first week of starting treatment, I noticed I had a little more spring in my step. After 10 days, there was a marked improvement in the size of my lymph glands. And after six weeks, my tumors were no longer detectable by physical exam."

STEVE FISCH

Tait Shanafelt said the study showed that the treatment is more effective and better-tolerated than traditional chemotherapy.

The researchers found that 89.4% of those participants who received the experimental drug combination had still not had leukemia progression about three years later versus 72.9% of those who received the traditional chemotherapy combination.

Difference in overall survival rate

They also saw a statistically significant difference in overall survival between the two groups; 98.8% of the people randomly assigned to receive the new drug combination were alive after three years versus 91.5% of those who had received the traditional treatment.

Although the incidence of serious treatment-related adverse events was similar between the two groups, infectious complications occurred more frequently in the group receiving the traditional treatment.

"I have two children, and I thought carefully about participating in a clinical trial," Rosenbaum said. "But when I learned that the traditional treatment carries a small but not insignificant mortality risk due to secondary infections, the decision became more clear. I've experienced minimal side effects from the combination of ibrutinib and rituximab that have been very manageable. It's been a life-changing experience."

"This is one of those situations we don't often have in oncology," Shanafelt said. "The new treatment is both more effective and better tolerated. This represents a paradigm shift in how these patients should be treated. We can now relegate chemotherapy to a fallback plan rather than a first-line course of action."

Steven Coutre, MD, professor of hematology at Stanford, is also a co-author of the study. ISM

OBITUARY

Christian Guilleminault, prominent sleep researcher, dies at 80

By Mandy Erickson

Christian Guilleminault, MD, DM, DBiol, a sleep expert at the School of Medicine who co-founded the journal *Sleep,* first described obstructive sleep apnea syndrome and helped establish the Stanford Sleep Medicine Center, died at Stanford Hospital July 9 with his wife, Priscilla Grevert, by his side. He was 80.

The cause was complications from metastatic prostate cancer.

Guilleminault helped expand Stanford's sleep clinic into a full-service center now known as the Stanford Sleep Medicine Center. He was also a prolific researcher who co-authored more than 800 journal articles on narcolepsy, sleep apnea, sudden infant death syndrome, snoring and other mostly sleep-related topics.

Christian Guilleminault

"He was just tireless," said Clete Kushida, MD, PhD, professor of psychiatry and behavioral sciences at Stanford and a colleague of Guilleminault's since 1994. "He would often be the first person to arrive at our labs, and he would be the last person to leave. He was always very interested in furthering sleep medicine and exploring sleep research."

'Transformative work'

Lloyd Minor, MD, dean of the School of Medicine, said that Guilleminault played a critical role in the advancement of our knowledge about sleep.

"Through contributions as a clinician and scientist, Dr. Guilleminault helped pioneer the field of sleep medicine," Minor said. "His transformative work will live on through the world-renowned Stanford Sleep Medicine Center, his innovative research and the many students and colleagues he mentored."

Guilleminault was born in 1938 in Marseilles, France. After earning a medical degree at the University of Paris, he completed residencies in psychiatry and neurology.

He came to Stanford in 1972 as a visiting assistant professor and became associate director of Stanford's sleep clinic, which had opened in 1964. It was the world's first clinic to focus on narcolepsy. He joined the faculty in 1980 and became a tenured professor in 1994.

William Dement, MD, PhD, professor emeritus of psychiatry and behavioral sciences, said Guilleminault "changed the world."

"We worked to make sleep-disorders medicine a legitimate clinical specialty, presented courses for practicing physicians, established reimbursement for sleep testing, and worked hard to bring narcolepsy and sleep apnea to the forefront of sleep medicine practice," Dement said. "I feel extremely fortunate that he chose Stanford."

Guilleminault became interested in sleep research after studying a kind of epilepsy that appears during sleep, according to Dement. Although Guilleminault studied narcolepsy, insomnia, the physiological and endocrinological changes that take place during sleep, and other sleep-related issues, much of his research focused on sleep apnea.

He coined the term obstructive sleep apnea syndrome to describe episodes during sleep when the upper airway collapses, reducing blood oxygen levels and disrupting sleep. Guilleminault also recorded the condition in children, finding a correlation between sleep apnea and learning and attention disorders. He and Dement devised the apnea-hypopnea index, which is used to diagnose and rate the severity of the condition.

In 1977, Guilleminault and Dement founded the journal *Sleep*, the official publication of the Sleep Research Society. Guilleminault served as editor-in-chief until 1998.

"We will dearly miss Dr. Christian Guilleminault," said Laura Roberts, MD, professor and chair of psychiatry and behavioral sciences. "He was a giant in the field of sleep medicine, an inspiring colleague, a beloved mentor, an interdisciplinary scholar and a champion for patients whose suffering was immense but poorly understood."

'He really listened'

Kushida said Guilleminault was "an excellent teacher" and "very good with patients. He really listened. You could just feel the intensity of him looking at you and studying you, trying to connect the dots."

Kushida added that Guilleminault had a sharp wit, often joking that students would find themselves in a guillotine if they didn't meet his expectations. A connoisseur of wine and cheese, he served both at informal lab parties. Dement remembers a meeting in Europe that the two of them attended: "We turned it into a great wine-tasting event."

In addition to his wife, who lives in San Francisco, Guilleminault is survived by two sons, Eric Guilleminault of Scottsdale, Arizona, and Damian Guilleminault of Paris, France.

The family is planning a memorial service. Donations may be made in his honor to the American Sleep Apnea Association. ISM

Arthritis

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done well on other therapies, these findings are cause for optimism, enthusiasm and hope," said Mark Genovese, MD, professor of immunology and rheumatology and principal investigator of the study.

Stanford Health Care offers services to rheumatoid arthritis patients through its immunology and rheumatology clinic. As clinical chief, Genovese spends three half-days per week in the clinic, where he regularly sees and treats rheumatoid arthritis patients.

He is the paper's lead author. The senior author is Tsutomu Takeuchi, MD, PhD, professor of rheumatology and clinical immunology at Keio University School of Medicine in Tokyo, Japan.

Rheumatoid arthritis is a progressive, systemic autoimmune disease affecting at least 1 in every 100 people worldwide. For reasons that aren't understood, 3 of every 4 people with the disorder are women. While its most visible hallmarks are pain, stiffness, inflammation and eventual deterioration of joints, patients also are at heightened risk for cardiovascular disease and other inflammatory complications.

In clinical trials, about 70% of rheumatoid arthritis patients have appeared to benefit initially from small-molecule therapies in a pill form, such as methotrexate, said Genovese, who is the James W. Raitt M.D. Professor. However, "in the real world, adherence to any of them is more like 50%," he said. Patients for whom the conventional small-molecule drugs fail are switched to pricey, injectable, bioengineered-protein drugs, including three of the world's top-grossing drugs. But these drugs, too, fail among about half the rheumatoid arthritis patients who use them, Genovese said.

Selective JAK-1 inhibitor

The experimental compound, filgotinib, is a selective JAK-1 inhibitor. It works by preferentially blocking 1 of a set of 4 closely related enzymes required for certain inflammatory signaling processes within cells. Two other compounds that are similar in mechanism of action to filgotinib but that impede JAK enzyme family members less selectively are licensed in the United States for use by rheumatoid arthritis patients, but only at low doses or with warning labels due to side effects.

The trial was conducted in 114 centers in 15 countries, mostly in North America and Europe. The 449 participants averaged 56 years of age, and about 80% of them were female. They were randomized to 1 of 3 study arms, in which they received daily doses of either 200 milligrams of filgotinib, 100 milligrams of filgotinib or a placebo for 24 weeks. All participants had moderately to severely active rheumatoid arthritis despite treatment with one or more biologic therapies.

The primary goal of the study was to observe whether there was an improvement, at 12 weeks into the trial, of at least 20% on a measure of joint swelling and tenderness called the ACR20 that was established by the American College of Rheumatology. An important secondary outcome was a score indicating low disease activity in 28 predetermined joints on a test called the DAS28-CRP.

Compared with the placebo group, a significantly greater proportion of participants on both the high- and low-dose filgotinib regimens achieved the primary endpoint: a 20% improvement in symptoms as measured by the ACR20. Sixty-six percent of participants on 200 milligrams of filgotinib, and 57.5% of those on 100 milligrams, fulfilled this criterion, versus only 31.1% of those on placebo.

Of equal or even greater importance, Genovese said, was the participants' improvement on the DAS28-CRP at both 12 and 24 weeks. By 12 weeks, 40.8% of those on the 200 milligram dose of filgotinib and 37.3% of those on 100 milligrams had reached the status of low disease activity as measured by the DAS28-CRP, as opposed to only 15.5% of those on the placebo regimen. These outcomes continued or improved over the course of the trial. By 24 weeks, 48.3% of the high-dose filgotinib recipients and 37.9% of those on the low dose had reached low-disease-activity status.

NORBERT VON DER GROEBEN

Mark Genovese led an international clinical trial of an experimental medication that improved the condition of rheumatoid arthritis patients who had failed to get relief from other therapies.

By week 12 of the trial, 22.4% of high-dose and 25.5% of low-dose filgotinib recipients, but only 8.1% of placebo recipients, had DAS28-CRP scores indicating outright remission. By week 24, high-dose recipients had a remission rate of 30.6%; low-dose recipients, 26.1%; and placebo recipients, 12.2%.

Improvement seen early on

The drug's benefits to participants became apparent soon after the trial's onset. "We could see improvements as early as two weeks into the trial," Genovese said.

Also telling was a substantial difference among the study arms in how many participants completed the 24-week trial. Of the 148 participants in the placebo arm, 51 dropped out before completion. Only 20 of the 148 high-dose recipients and 34 of the 153 low-dose recipients dropped out.

Investigators' early concerns about increased susceptibility to infections, or the re-emergence of active forms of prior infections, such as tuberculosis or shingles, were assuaged by the relative smattering of such adverse events, compared with placebo.

Notably, patients for whom at least three different biologic therapies provided insufficient relief did as well in this trial as those who'd derived insufficient relief from just one biologic therapy, Genovese said. "We found that those high levels of response were independent of how many drugs you'd failed, and independent of which drugs you'd failed," he said.

Overall response rates to filgotinib appear to surpass those of the other commercially available JAK inhibitors at doses approved for use in the United States, he said.

"This novel drug works exceptionally well in patients who've already failed traditional therapies for rheumatoid arthritis," he said.

The trial was funded by Gilead Sciences, a biopharmaceutical company that holds the rights to filgotinib. The company has announced its intention to file for Food and Drug Administration approval of the drug.

Genovese is a consultant for Gilead.

Stanford's Department of Medicine also supported the work. ISM

Joint Commission lauds SHC for quality and transparency

By Amy Jeter Hansen

Notification appeared via secure website around 7:15 a.m. on June 17. Glued to their smartphones, as they had been every Monday morning for 18 months, Stanford Health Care's Accreditation, Regulatory and Licensure group sprang into action.

At 7:20 a.m., senior quality consultant Catherine Sun sent an email alerting more than 880 employees:

"The Joint Commission has arrived!"

STANFORD HEALTH CARE

The Joint Commission conducted its triennial accreditation survey of Stanford Health Care earlier this summer.

It was the beginning of a five-day journey that would span the entire Stanford Health Care enterprise, including the main hospital and dozens of ambulatory clinics. Nine surveyors from one of the nation's oldest and most respected health care accreditors had dropped in to conduct their customary, painstaking review of compliance with patient safety and quality standards — an on-site evaluation that happens every three years for accreditation renewal.

Stanford Health Care's showing was particularly impressive this time around, said president and CEO David Entwistle. "We had one of our top surveys yet," he said. "Not only did we demonstrate meticulous adherence to safety and quality standards, but the surveyors also lauded our culture of transparency — how helpful we were on an ongoing basis, how quickly we completed tasks, how responsive we were to what they needed."

Accreditation from The Joint Commission certifies that a health care organization continues to meet or exceed meticulous procedural standards that align with government requirements, making the organization eligible for reimbursement through Medicare and Medicaid. It also signals a hospital's commitment to developing and adhering to rigorous policies governing everything from provision of care to food preparation to data management.

"Having surveyors in here, helping us to see ourselves more clearly, is a good thing, and we take that feedback from The Joint Commission very seriously," said Quinn McKenna, Stanford Health Care's chief operating officer. "We want to be on the top decile as a leading major academic medical center in the country with regards to quality, safety and patient outcomes. And getting a strong, good survey is part of that journey."

Setting health care standards

Based in Illinois, The Joint Commission is an independent, nonprofit organization that for nearly seven decades has set health care standards based on expert consensus and scientific literature, and evaluated organizations' compliance with those standards.

The survey itself is a grueling process; its scope is comprehensive. Surveyors may visit any area, ask questions of any staff member at any time and request documents and other information related to the survey.

To manage logistics, Stanford Health Care leaders set up a survey operations center for the week. Each of the nine surveyors was accompanied by an escort and scribes, and liaisons from Stanford Health Care were assigned to assist.

"Approximately 100 patient medical records were reviewed by the surveyors, along with numerous policies and procedures, and employee files. In addition, the surveyors spoke with 464 staff members," Sun said.

Stanford Health Care administrators, physicians and staff participated in presentations and discussions on such topics as leadership, data management, infection prevention and medication management. Surveyors also could take a deep dive into specific areas using a "tracer" methodology: They could focus on one topic, such as medication administration, across the organization, or they could follow a randomly selected patient's journey from admission to discharge.

"It's a very fluid process," said Maureen Doherty, RN, manager of accreditation and regulatory affairs. "Some of the surveyors may have an initial plan or focus in mind, but then decide to change plans based on what they have seen. We have to be prepared and nimble in accommodating their requests across the organization, and that requires excellent communication across a well-coordinated team."

Praise from surveyors

Shortly after the survey, Stanford Health Care leaders learned that the organization's accreditation had been renewed. Mark Pelletier, RN, The Joint Commission's chief nursing executive and chief operating officer for accreditation and certification operations, provided this written comment: "We commend Stanford Health Care for its continuous quality improvement efforts in patient safety and quality of care."

As is customary, comments from the surveyors were offered verbally, and Stanford Health Care officials reported that the surveyors were pleased with what they saw — even noting areas in which Stanford is a model for other organizations. In particular, surveyors praised kitchen services, the use of data for improvement and the scope and scale of ambulatory care services.

"When they came to our clinics and our units, there were teams of people waiting to show them around and talk with them," said Lisa Schilling, RN, vice president of quality, safety and clinical effectiveness. "The attitude, the leadership, the seriousness and the collegiality that we offered was really notable to them."

Norman Rizk, MD, chief medical officer, characterized the survey as "a very good visit" but cautioned against becoming complacent. Surveyors will return to evaluate the new Stanford Hospital, potentially as soon as the day after it opens.

"The goal generally is to become the best at getting better," Rizk said. "It's our responsibility to the public — and to each other." **ISM**

OF NOTE

reports on significant honors and awards for faculty, staff and students

FRANCIS BLANKENBERG, MD, associate professor of pediatric radiology; **KATHERINE FERRARA**, PhD, professor of radiology; and **TARIK MASSOUD**, MD, PhD, professor of radiology, were among the 37 researchers who received the 2019 Distinguished Investigator Award from the Academy for Radiology & Biomedical Imaging Research. The award acknowledges and celebrates high levels of achievement in the field of academic imaging research.

SCOTT BOYD, MD, PhD, associate professor of pathology; **MICHELLE MONJE**, MD, PhD, associate professor of neurology and neurological sciences; and **CAROLYN RODRIGUEZ**, MD, PhD, associate professor of psychiatry and behavioral sciences, are recipients of the Presidential Early Career Award for Scientists and Engineers. The award is the highest honor bestowed by the U.S. government to outstanding scientists and engineers who are beginning their independent research careers and who show exceptional promise for leadership in science and technology.

Francis Blankenberg

Katherine Ferrara

Tarik Massoud

Scott Boyd

LISA CHAMBERLAIN, MD, MPH, was promoted to professor of pediatrics, effective June 1. Her research explores health inequities, specifically for low-income pediatric populations in California. She focuses on children with chronic illness. She is the associate chair of policy and community engagement in the Department of Pediatrics.

TARA CHANG, MD, was promoted to associate professor of medicine, effective May 1. Her clinical research focuses on cardiovascular disease in patients with chronic kidney disease, with an emphasis on blood pressure control, coronary revascularization and the comparative effectiveness of cardioprotective medications. Her long-term goal is to improve outcomes in these high-risk patients.

LORINDA CHUNG, MD, was promoted to professor of medicine, effective April 1. She specializes in caring for patients with systemic sclerosis and related diseases. Her research investigates treatments for systemic sclerosis and the pathogenesis of the disease.

MARIA INMACULADA COBOS SILLERO, MD, PhD, was appointed assistant professor of pathology, effective June 1. Her lab uses single-cell methods to gain insight into the cellular and molecular mechanisms underlying Alzheimer's disease and other dementias.

DANA HAERING, chief financial officer of Lucile Packard Children's Hospital Stanford, and **LINDA HOFF**, chief financial officer of Stanford Health Care, are included in *Becker's Hospital Review*'s list of 106 CFOs to know in 2019. Nominations and selections were made through an editorial review process.

VIVIANNE TAWFIK, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine, has been awarded a 2019 Rita Allen Foundation Award in Pain grant. The three-year, $50,000 per year award will support her research into the unique underpinnings of various types of chronic pain and how central nervous system glial cells (astrocytes and microglia) contribute to the transition from acute to chronic pain.

BRAD ZUCHERO, PhD, assistant professor of neurosurgery, received a 2019 Beckman Young Investigator award from the Arnold and Mabel Beckman Foundation. The award, which includes $600,000 in funding over four years, is given to promising young faculty members in the early stages of their academic careers in the chemical and life sciences. Zuchero will use the award to support his study of novel roles of myelination in the development, function and diseases of the nervous system. **ISM**

Michelle Monje

Carolyn Rodriguez

Lisa Chamberlain

Tara Chang

Lorinda Chung

Maria Inmaculada Cobos Sillero

Dana Haering

Linda Hoff

Vivianne Tawfik

Brad Zuchero