Neuron-stimulated mice see what isn’t there

By Bruce Goldman

Hallucinations are spooky and, frighteningly, 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, is significant 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 scientist James Marshel, PhD, and Sean Quinn, PhD; graduate student Yoon Seok Kim; and postdoctoral scholar Timothy Machado, PhD.

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-dot 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” the 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 illusory images in the animals’ minds.

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.

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 in-jecTABLE biological drugs saw substantial improvement in their condition from daily use of an experimental drug.

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

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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 deactivate 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 expressed 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 and molecular biology, was the senior author. John Stanford Institute for Stem Cell Biology and Regenerative Medicine and director of the Ludwig Center for Cancer Stem Cell Research, was the senior author.

“Finding that not all patients responded to anti-CD47 antibodies helped fuel our research at Stanford to test whether non-responder 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 protein that is keeping them safe 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 stuffed with cancer cells,” Barkal said.

The researchers then 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 cancers, both of which are very hard to treat, were highly affected by blocking the CD47 signal while tumors that are more responsive to PD-L1 signaling were less affected. “Some cancers, like blood cancers, seem to be highly susceptible to CD47-signaling blockade, but not to PD-L1-signaling blockade. In other cancers, like ovarian cancer, the opposite is true,” Barkal said. “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 CD47 signaling will allow them to test other cancers for 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 life-saving 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 Kowarski; and doctoral scholars Balyon Zaro, PhD, and Jason Hatakeyama, PhD; Layla Barkal, MD, PhD, resident physician in internal medicine; Venkatesh Krishnan, PhD, associate professor of obstetrics and gynecology; and Oliver Dorigo, MD, PhD, associate professor of obstetrics and gynecology.

S.ETHAN GROEBEN

Malignant cells may evade the immune system by blocking a natural signal.”

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.

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 explore oncology service opportunities. The intent of the collaboration is to improve access for patients in the East Bay and to increase the 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 and their families—to the extent possible by building on the strength of Stanford’s leadership in translational research, clinical care, and national, 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 patients. “A collaboration between Sutter and Stanford is a natural fit,” said Julie Petrine, 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.”

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Send letters, comments and story ideas to John Sanford at 723-8309 or at johnsanford@stanford.edu.

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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 Stanford Medicine.

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

“While the research published online July 17 in Nature suggest that existing drugs could one day be repurposed to 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 makes 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 nation’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. Sutter Health 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.

Oncology

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

“Working with Sutter Health in the East Bay will bring new hope for cancer patients in some of the world’s most important cancer treatment trials,” said Lloyd Minor, MD, dean of the Stanford School of Medicine and president of Stanford Medicine. “I think it’s going to be an opportunity for patients and their families who are seeking treatment for cancer and its side effects. Stanford Medicine’s physician-scientists are actively investigating new treatments and technologies, and I want 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 makes more discoveries.

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

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 a typical or obvious candidate for regulating heart function.

“We were puzzled,” said Wu, the Si- mon F. Marquis, MD, Professor of Medicine and of Radiology.

“Why would a mutation in a nuclear scaffold protein that is 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 tissues are another option, 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 be differentiated into heart muscle cells 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 them 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 were on or off in cells with the mutation — and what they could do about it.

"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 planter-derived growth factor, or PDGF, pathway. When the researchers tested heart tissue from laminopathy 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, cre nondanub and suniitnib, 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.

“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 CaH-M, the Stanford Cancer Institute and the Stanford Maternal & Child Health Research Institute.

Other Stanford co-authors of the study are postdoctoral scholars Ilanit Ichhaki, PhD, Joe Zhang, MD, PhD, Xingsi Chen, PhD, and Isaac Pereia Gal, PhD; instructors Chi Keung Lam, PhD, Edward Lau, PhD, and Haodi Wu, PhD; former postdoctoral scholars Priyanka Garg, MD, Timon Streger, MD, and Jared Churko, PhD; graduate student Mohamed Aneen; Karim Sallam, MD, clinical assistant professor of medicine; clinical instructor June-Wahe Rhee, MD; research assistant Tony Chour; former research assistant 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 Californian 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.
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 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 these aggregates are made, and potentially how we can hinder that process.”

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 Shi-zuka Yamada, a graduate student in Gitler’s lab. There, too, inhibiting the gene helped ramp 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 disease-instructive 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 slue 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 the proteins come to be anyway.”

During run-of-the-mill protein formation, the ribosome is 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 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 at monitored for changes in a fungal 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 toxic protein levels when they tested how neurons derived from patients with ALS fared without RPS25.

“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.”

Further, Yamada and the team now is investigating how a more complex animal model — like a mouse with the ALS mutation — would fair without RPS25. “With the fruit flies, we tampered with the gene; we didn’t remove it completely,” Yamada said. “But an animal can survive without the gene entirely as a big part of our next step.”

Furthermore, Yamada said, she and Gitler are still at a clearer picture of RAN translation in humans, overall. “Does it only occur under neurogenetic conditions? Or is this 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 Ge-nuth and Nicholas Kramer; postdoctoral scholar Rosolyn Grossky, PhD; research technician Lisa Nakayama; high school student Shireen 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.

School readiness impaired in preschoolers with ADHD symptoms

By Erin Digitaile

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 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 ready or develop school readiness problems in the years even in children who don’t 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. The rest were identified by their parents having significant concerns about the 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, the child’s ability to prioritize actions and tasks and exercise self-control to regulate behavior and meet long-term goals.

Children were considered impaired in an area of functioning if their assessment scores fell below the 25th percentile.
Children with ADHD were no more likely than their peers to show signs of poor diet and lack of exercise compared to their peers without ADHD, as suggested by previous research. They were 73 times more likely than children without ADHD to be impaired in approaches to learning. They were twice as likely to be considered unready for school if they were impaired in two or more of the five areas of functioning measured in the study. This area of study is under-studied.

Researchers have known that smooth muscle cells reinvent themselves during atherosclerosis. Quertermous and Wirka, however, said that their team wasn’t sure what their identity was. Scientists thought these cells could have a beneficial role, but also suspected they could transform into cells that no longer recognize themselves as immune, smooth muscle, fibromyocyte and more — and reproduce arterial plaque.

For these cells, the identity shift happens in a disease called atherosclerosis. It occurs when arteries get clogged by plaque, a buildup of fats, cholesterol and molecular particle. Plaque grows within the layers of tissue that form the artery, narrowing the blood conduit to too small for the blood to pass through. Too much plaque tears open the tissue, allowing the buildup to enter the bloodstream.
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 National Center for Advancing Translational Sciences to fund the Stanford Clinical and Translational Science Awards (CTSA) program, which will bring the total awarded to $106 million since the program was founded.

The CTSA Program is overseen by the National Center for Advancing Translational Sciences at the National Institutes of Health. The Stanford program is led by Stanford Dean of Research and the Stanford School of Medicine’s senior associate vice provost for research, Mark Cullen, MD.

This renewal will continue Stanford’s collaborations with a national network of 50-plus academic medical research institutions, known as CTSA Program hubs. These 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 other hubs.
• 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 health and well-being of individuals and populations. The funding will support the school’s efforts to develop 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 Programs. Stanford’s funding will help to build a national network of 50-plus academic medical research institutions, known as CTSA Program hubs. These hubs work together to share resources and improve the processes that turn research discoveries into medical treatments and cures.

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 Predictr and Diagnosics Accelerator, a program that assists efforts to research, develop and deploy technologies for improving diagnoses and better predicting the progression of diseases.
• A data science resource portal from which researchers can access advanced tools and data platforms and to analyze and derive insights into ways to conduct 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 metadata and imaging data. This system enables researchers to gain collaborative access to unused biopspecimen and related data for use in identifying new underserved populations.
• 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 https://ctsa.nih.gov. More information about Stanford’s CTSA program, visit the Spectrum website at http://med.stanford.edu/spectrum.html.

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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 tell the difference grew, they became more and more likely to fire in response to a horizontal bar.

Hallucinating mice

Once the mice had become adept at discriminating between horizontal and vertical bars, the scientists trained them to lick tubes 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 receiving 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 demonstrated that optogenetically stimulating these neurons optogenetically. Once the mice were trained, optogenetically stimulating neurons containing just a few of these neurons was enough to get them to respond with appropriate licking or non-licking behavior.

The researchers were surprised to find that optogenetically stimulating just 10 to 20 neurons — or fewer in some cases — selected only for being responsive to the right orientation could produce the same neuronal activation 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 in our brains? The answer is that the mammalian cortex is somehow poised to respond to an amazingly low number of neurons without causing perceptual perceptions in response to noise." Deisseroth is a member of Stanford Bio-X and of the Wu Tsai Neurosciences Institute.

Leukemia continued from page 1

threatening infections that are difficult for many patients to tolerate.

Rituximab plus ibritinib

The new drug combination pairs rituximab with another drug, ibritinib, 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 ibritinib and rituximab, followed by rituximab 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 consisting of the drugs fludarabine, cyclophosphamide and rituximab. hut who were randomly assigned to receive the experimental treatment, until they had still not had leukemia progression about three years later versus 72.9% of those who received the traditional chemotherapy combination.

Disease 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 chemotherapy combination. Although the incidence of serious treatment-related adverse events was similar between the two groups, including infection, they were less common among patients currently 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 with the new combination of ibritinib and rituximab that have been very manageable. It’s been a life-changing experience.”

This is one of those situations in oncology,” Shanafelt said. “The new treatment is both more effective and better tolerated. This represents a major step forward in how these patients should be treated. We can now reconcile chemotherapy to a full-blank plan rather than a first-line course of action.”

Steven Couture, MD, professor of hematology at Stanford, is also a co-author of the study.
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, 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. Along the way, he co-authored more than 800 journal articles on narcolepsy, sleep apnea, sudden infant death syndrome, snoring and other mostly sleep-related topics.

“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 lab, 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 elucidated the role of obstructive sleep apnea in the development of a variety of health conditions and he helped develop the first full-service sleep center in medicine in the United States.”

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 sees patients for bioengineered-protein drugs, in addition to other biologic therapies for rheumatoid arthritis patients.

He is the paper’s lead author. The study is the largest of its kind ever conducted at Stanford Sleep Medicine Center, his innovative research and the many students and colleagues he mentored.

Guilleminault was born in 1938 in Marseille, 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 1995.

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

“We worked to make sleep disorders not just a legitimate clinical specialty, presented courses for practicing physicians, established reimbursement for sleep treatment, and worked hard to battle 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.

Genovese revised 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 1999.

“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 inspired teacher, 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 in which 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.
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 Licensee 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!”

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,” said president and CEO David Entwistle. “We had one of our top surveys yet,” said president and CEO David Entwistle. “We had one of our top surveys yet,” said president and CEO David Entwistle. “We had one of our top surveys yet,” said president and CEO David Entwistle. “We had one of our top surveys yet,” said president and CEO David Entwistle. “We had one of our top surveys yet.”

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.

“I’ve been involved with many ‘tracers’ over the years,” 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 to drive improvement and the scope and scale of ambulatory care services.

“Some of the areas that really stood out to us in 2019 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 collegiability that we offered were notable features,” Sun said.

Norman Rink, 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,” Rink said. “It’s our responsibility to the public — and to each other.”

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

Although quality and safety leaders were pleased with how quickly we completed the survey, how responsive we were to them when we 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. 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.

LISA CHAMBERLAIN, 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 women 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 IMMACULADA 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 anesthesia, 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 neuronal glutamergic (alpha- and microglial) contribute to the transition from acute to chronic pain. Zuchero will use the award to support his study of novel roles of myelin in the development, function and diseases of the nervous system.

Brendan Zuchero