INSIDE STANFORD MEDICINE

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Scientists have revealed the beautiful and efficient mechanism that allows starfish larvae to survive to adulthood.

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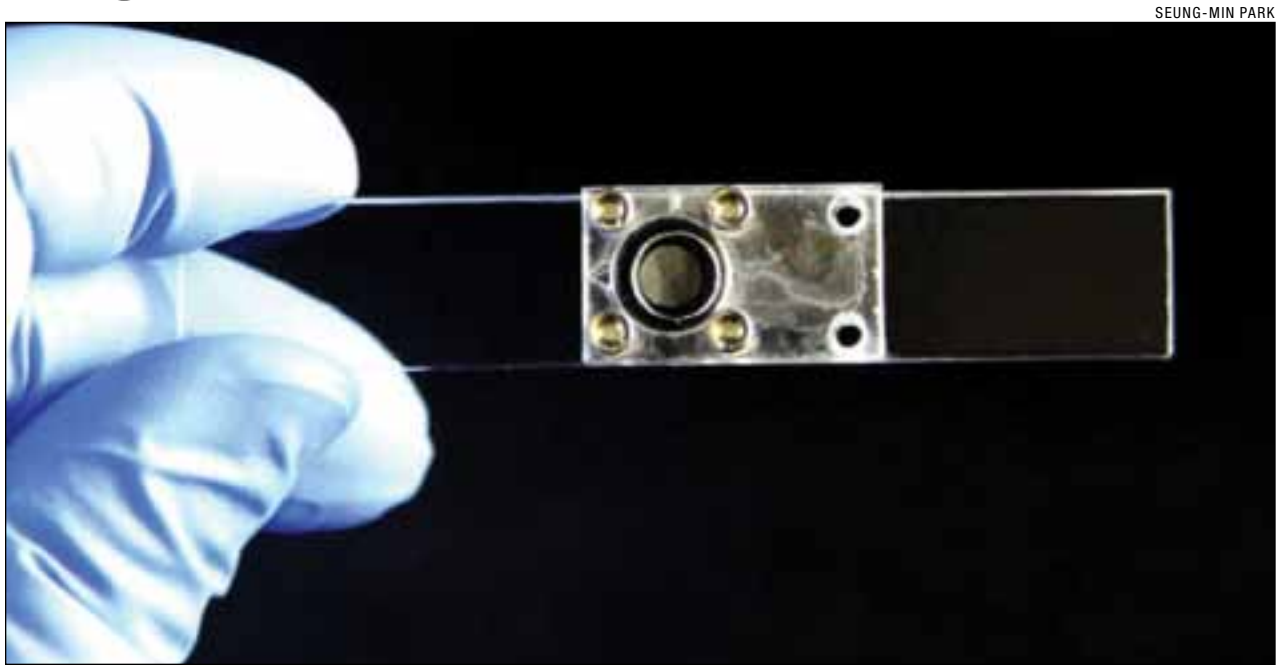
Blood test for lung cancer tumors developed

By Jennie Dusheck

SEUNG-MIN PARK



A MagSifter chip, shown here fastened to an acrylic holder, was used to purify circulating tumor cells from the blood of lung cancer patients.

Profiling the genes of tumor cells from lung cancer patients' blood samples may be a cheap, noninvasive way to help doctors choose the right treatments, according to a study led by researchers at the School of Medicine.

The new findings strengthen the hope that evaluating the genetic profiles of tumor cells circulating in the bloodstream could transform cancer care: first, by indicating the next chemotherapy or targeted therapy to use when tumors evolve resistance to previous drugs; and, second, by providing a way to study how tumors change over time. The new blood test is safer, cheaper, faster and more effective than alternative diagnostic approaches, said the researchers.

The researchers created a system for isolating circulating tumor cells from the blood of cancer patients and reading a handful of genes from inside each tumor cell. Thus, they were able to obtain genetic information about the original cancer tumor that resides deep in the lungs without doing a biopsy, which can be dangerous for the patient.

"We are trying to make minimally invasive technology that allows us to continuously monitor one person's health over time," said radiology instructor Seung-min Park, PhD, a lead author of the new study, which was published online Dec. 12 in the *Proceedings of the National Academy of Sciences*. Park shares lead authorship of the study with former Stanford graduate students Dawson Wong, PhD, and Chin Chun Ooi.

Tumor changes

It's common for cancer therapies to fail after a few months, often because the cancer evolves resistance to the treatment. At that point, it's important to understand how the patient's tumor is changing. "Without a biopsy and genetic profiling, we are flying blind, trying to select a second or third option for therapy and hoping it works," Park said. But repeated lung biopsies are too hard on patients. Even CT scans, performed to see whether a tumor is shrinking or growing, increase the body's exposure to damaging X-rays. "Blood-based monitoring would allow us to select the right second and third therapies instead of flying blind," he said.

Finding a way to look at circulating tumor cells, or CTCs, in the blood has been a goal of oncologists for years. When people die of cancer, it's usually from metastasis, the spread of tumors throughout the body. Part of metastasis is the entry of tumor cells into the bloodstream, where they circulate along with normal blood cells, eventually landing in other organs and initiating tumors there. In general, the presence of CTCs in the blood predicts that cancer patients will live for a shorter time.

"This work fits well into our bigger vision of using blood-based diagnostics to detect and manage disease, including cancer," said Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology and the Virginia and D.K. Ludwig Professor in Cancer Research. "By being able to characterize single CTCs, we believe cancer management, including predicting response to therapy, will be much better optimized."

Gambhir shares senior authorship of the study with Shan Wang, PhD, professor of materials science and engineering and of electrical engineering, and Viswam Nair, MD, clinical assistant professor of medicine and of radiology.

How it's done

The blood typically contains very few CTCs, so one of the challenges for oncologists has been to separate them from ordinary blood cells. The new technique involves taking blood from lung cancer patients and then attaching antibodies to circulating tumor cells. Once the cancer cells are labeled, the team introduces magnetic nanoparticles designed to attach to the antibodies labeling the cancer cells. With each individual cancer cell labeled with a magnetic nanoparticle, the researchers can then use a device called a magnetic sifter, or MagSifter, previously developed by Wang.

The MagSifter is an electromagnetic sieve that can be turned on and off. When the MagSifter is on, it pulls the nanoparticle-labeled

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Research locates absence epilepsy seizure 'choke point' in the brain

By Bruce Goldman

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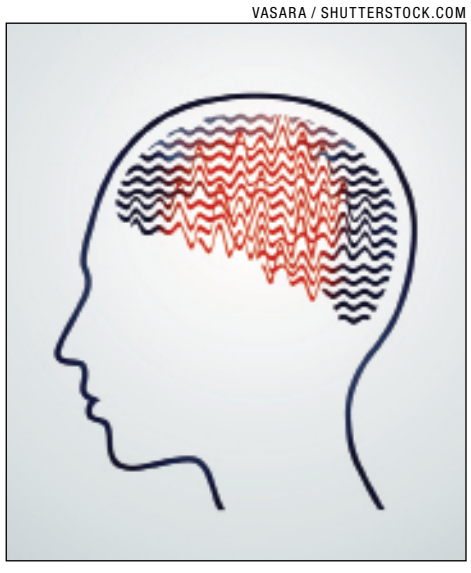


A particular structure in the brain is a "choke point" for a type of epileptic seizure that affects mostly children, School of Medicine investigators have found.

The researchers used an advanced technology called optogenetics to show, in rodent models of one of the most common forms of childhood epilepsy, that inducing synchronized, rhythmic activity in a specific nerve tract within this structure is sufficient to cause seizures, while disrupting that activity is sufficient to terminate them.

Epilepsy, a pattern of recurrent seizures, affects about 1 in 26 people over their lifetime, said John Huguenard, PhD, professor of neurology and neurological sciences and of molecular and cellular physiology. Absence, or petitmal, seizures — a form of epilepsy most likely to occur among children ages 6-15 — account for about 1 in 20 cases of epilepsy. They are characterized by a sudden loss of consciousness, accompanied by a behavioral and postural freezing in place that typically persists less than 15 seconds. A child experiencing an absence seizure usually has no recollection of it.

"These seizures can be so subtle that they go unnoticed or are mistaken for a lack of attention," Huguenard said.

The new findings, described in a study published

See EPILEPSY, page 6

Smartphones could be game-changing tool for cardiovascular research, study shows

By Tracie White

Widespread ownership of smartphones around the world could potentially transform cardiovascular research by providing rapid, large-scale and real-time measurement of individuals' physical activity, according to a new study by researchers at the School of Medicine.

"People check these devices 46 times a day," said Euan Ashley, DPhil, MRCP, associate professor of cardiovascular medicine. "From a cardiovascular health standpoint, we can use that personal attachment to measure physical activity, heart rate and more."

Ashley is senior author of the study, which was published Dec. 14 in *JAMA Cardiology*.

In March 2015, Stanford researchers launched a free iPhone app — MyHeart Counts — which gave users the ability to participate in a first-of-its-kind, easy-to-use cardiovascular research study. The app uses Apple's ResearchKit framework, which gives potential users a simple way to consent to participate, measure daily activities, complete tasks and answer surveys through their iPhone. Within six months of the app's launch, researchers had enrolled 47,109 participants from all 50 states who had consented to participate in the study.

Within weeks, researchers were able to collect data from 4,990 participants who completed a six-minute walk fitness test using the phone's built-in motion sensors — a number several times larger than the largest study previously published, the

See HEART, page 4

NORBERT VON DER GROEBEN

Within six months of its launch, the MyHeart Counts app had more than 47,000 users who had agreed to participate in a study tracking their heart health.

Tech support at medical school gets 'lean,' raises the bar for service

By Kris Newby

It's 10 a.m. Monday, time for the lean team huddle at the Information Resources and Technology office on Porter Drive. On this day, team members review progress on documenting the remote setup configurations of the hundreds of networked printers used at the medical school. It's a daunting task, but posting this resource online will enable support staff to more rapidly connect new computers to printers and reduce the need to send field technicians out to customer sites.

This is just one example of how IRT support technicians are applying the "lean" approach, made famous by Toyota and other organizations, to improve customer value by engaging team members to recognize and solve problems.

Eight months after IRT's first lean pilot project, results have been promising. Caller satisfaction is higher than ever, with 94 percent of survey respondents reporting positive experiences. And the average amount of time it takes for a caller to get a help-desk technician on the line is steadily improving, down from 112 to 24 seconds between August and November.

In addition to revamping its processes, the IRT group has upgraded its infrastructure and launched new customer-focused services. They've installed a state-of-the-art call system that displays help requests and wait times on large monitors around the office. When callers wait too long, their listings turn red, signaling help-desk technicians who are working on requests that aren't time-critical to lend a hand. They've also opened a walk-in tech support bar in the basement of Lane Medical Library, complete with loaner computers for employees whose own machines are being repaired.

Looking back over the last year, Jesse Mena, an IRT service technician and a lean team member, said, "There's been a revolutionary change in our approach to customer service."

The lean launch

Last March, the IRT group formed its first lean team to improve the efficiency in the help-ticket process. The project started with a three-day launch, attended by representatives from the help-ticket team and a lean consultant.

In the first phase, participants documented each step of the help-ticket process by posting sticky notes along a wall. At the end of the day, the team was surprised at the complexity of the work flow, illustrated with 15 feet of branching and looping sticky notes. The flaws in the process were laid bare, revealing that some help tickets had the potential to get stuck in the system for up to 40 days.

Next, the team learned how to integrate the lean process into the IRT work environment so that anyone with a good idea could write it on a sticky note and post it to a visualization board in the tech support area. During Monday huddles, ideas are discussed by all the team members, keeping in mind the lean mantra: "How can we quickly learn what ideas work, then discard the ones that don't?" If the group decides that an idea has merit, it is systematically moved through planning, testing and deployment phases. The weekly huddles create a mechanism that keeps subprojects moving and prevents good ideas from falling through the cracks.

KRIS NEWBY

Amber Burleigh, an IRT service desk technician, said she likes the way the lean process is slowly changing the way the organization identifies and fixes problems.

A bottom-up approach to problem-solving

Amber Burleigh, a service desk technician, said she likes the way the lean process is slowly changing the way the organization identifies and fixes problems. She said it's moving innovation from a top-down management approach to a bottom-up approach. Problems are identified and fixed by the people who understand them the best: those on the front lines of customer service.

Burleigh, who said that she'd never heard about lean until this year, admitted that it wasn't an easy sell in the beginning. "When we first started, we had trouble getting everyone on board," Burleigh said. "Some people don't like change."

But six months after the launch, the lean process has won over many naysayers within IRT. Ideas sparked by the lean launch have led to major improvements, such as better call-tracking reports and a new call-triage system that rapidly escalates complex questions to specialty technicians, reducing the average time a call lasts with a customer.

In addition, new ideas for improving employee satisfaction have been adopted, such as a board that highlights praise from customers in the common area and the establishment of an employee-of-the-month award to recognize superior service.

IRT's first experience with lean has been so encouraging that the office is launching a second project aimed at improving the medical school's IRT Service Desk performance. It is being led by Jesse Mena, an IRT service technician.

One of the first sticky-note ideas placed on Mena's Service Desk board was, "Benihanas dinner for team building." He said cultural onboarding is important as they grow their organization.

"The hard part is getting everyone to start putting ideas up," said Mena. "But once they see their own ideas move from plan to test to deploy, they get excited."

How your team can get lean

Encouraged by the success of the lean process, Marcia Cohen, the school's senior associate dean for finance and administration, has established a process-excellence team to help others at the school adopt this approach. The team's director, Bonnie Tsang, previously led lean improvement efforts at Lucile Packard Children's Hospital Stanford, and she is eager to assist other interested groups.

She acknowledged that there are unique challenges to establishing lean practices in academic settings. These institutions typically have complex organizational and decision-making structures and frequently need to balance multiple missions, she said.

Tsang is a soft-spoken, thoughtful evangelist for lean. Her job entails educating employees about lean, helping teams embrace change and motivating them to continuously improve. She adds, "Our motto is to empower innovation by every person every day."

To learn more, go to https://med.stanford.edu/fiscalaffairs/process-excellence-.html **ISM**

KRIS NEWBY

Lora Pertle of Information Resources & Technology walks by a visualization board that tracks the progression of ideas for improving services.

Could eating caviar be a 'risk factor' for having lots of money?

By Krista Conger

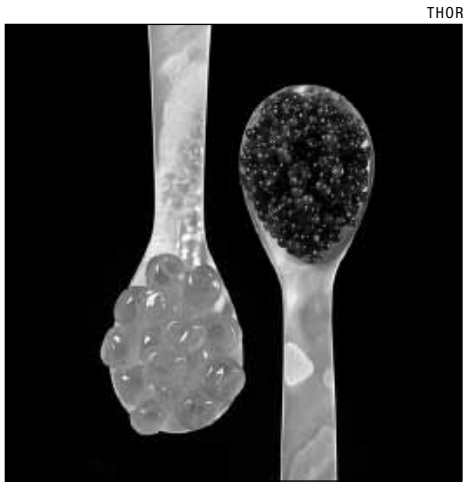
It was an hours-delayed flight and a $10 food voucher that did it.

Annoyed, Anders Huitfeldt, PhD, a postdoctoral scholar at the Meta-Research Innovation Center at Stanford, or METRICS, decided to spend his voucher on the most impractical item he could find in the airport. After some searching, he found it: a minuscule spoon of high-end caviar.

"It was the smallest amount you could possibly have," he said. "And it was wonderful. I kind of got addicted."

The experience got Huitfeldt thinking, but not just about fancy caviar. As a researcher at METRICS, he is interested in making scientific research findings more accurate and reproducible. "I have had a long-standing interest in trying to understand why published research papers often fail to find the truth," he said. "It seems that often researchers are confused about what they are actually trying to do."

THOR



Huitfeldt explored that problem in the *British Medical Journal*'s Christmas issue — a lighthearted collection of articles that address important scientific concepts. His piece, "Is caviar a risk factor for being a millionaire?," examines how the term "risk factor" can have at least four distinct meanings in scientific literature. For example, does caviar consumption predict current wealth (is it diagnostic)? Or the likelihood of amassing wealth in the future (prognostic)? Does it actually play a role in how wealth accumulates? (For example, does eating the fish eggs make you a stock-market wizard?) Or does the act of caviar consumption simply increase the probability of wealth, perhaps by bringing the consumer into close proximity of other wealthy movers and shakers with whom profitable deals can be struck? "The outcome of the study varies tremendously depending on what the researchers mean by 'risk factor,'" Huitfeldt said. "Until they agree, it's not even clear how the question should be addressed. And this uncertainty becomes a serious impediment to processing information correctly to arrive at the scientific truth."

For a more in-depth look at the many issues affecting research reproducibility, and the ways that Stanford scientists are attempting to address them, check out "Can you repeat that?" in the summer 2016 issue of *Stanford Medicine* magazine. **ISM**

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STANFORD MEDICINE

Some glioblastoma patients benefit from 'ineffective' treatment

By Krista Conger

A subgroup of patients with a devastating brain tumor called glioblastoma multiforme benefited from treatment with a class of chemotherapy drugs that two previous large clinical trials indicated was ineffective against the disease, according to a study at the School of Medicine.

Daniel Rubin

Specifically, patients in the subgroup who were treated with chemotherapy drugs that block the growth of new blood vessels in the tumor lived an average of about one year longer than those who were given other classes of chemotherapy drugs, the researchers found.

The retrospective study emphasizes the importance of properly categorizing tumors with varied biology in order to best personalize treatment for each patient. Lumping all glioblastoma patients together as one group led to the flawed conclusion that no patients benefited from anti-angiogenesis treatments, the researchers said.

"Traditionally, glioblastoma patients are given this diagnosis based on the histology of their tumor, and then assigned a grade and a stage," said Daniel Rubin, MD, associate professor of biomedical data science, of radiology and of medicine. "But this information is not always specific enough to clearly inform treatment. We've developed a new method of classifying glioblastomas by quantitatively analyzing the magnetic resonance imaging that is routinely performed during diagnosis."

Rubin is the senior author of the study, which was published online Dec. 22 in *Neuro-Oncology*. Postdoctoral scholar Tiffany Ting Liu, PhD, is the lead author of the paper.

A deadly brain tumor

Glioblastoma multiforme, also known simply as glioblastoma, is one of the most common, and most deadly, brain tumors. About 12,000 people in the United States are diagnosed each year with the disease. The median survival is about 15 months after diagnosis. Until recently, clinicians and patients pinned their hopes on a class of chemotherapy drugs called anti-angiogenic compounds that are meant to block the growth of new blood vessels into the tumor. Blocking this growth, they believed, should starve the tumors of oxygen and nutrients. However, two large, phase-3 clinical trials recently reported in *The New England Journal of Medicine* concluded that one such drug, bevacizumab, conferred no survival benefit on glioblastoma patients.

Liu, Rubin and their colleagues wondered if there might be a subgroup of glioblastoma patients that could still be helped by the treatment. They studied the medical records and diagnostic images of 69 glioblastoma patients who had been treated at a local medical center and 48 patients from a national database known as The Cancer Genome Atlas.

The researchers used specialized software to categorize each patient into one of two groups based on the degree of vascularization of the patients' brain tumors. Those whose tumors were more highly vascularized — as determined by an imaging technique called perfusion MRI — were significantly more likely to benefit from treatment with anti-angiogenic therapies than those whose tumors were less well vascularized.

Differences in glioblastoma biology

Perfusion MRIs are routinely conducted as part of the diagnostic procedure for brain tumor patients. The researchers found that each of the 117 patients fell neatly into one of two clusters: 51 of the patients had tumors that were highly vascularized, and 66 had tumors that were not as well vascularized. Further investigation showed that the highly vascularized tumors also expressed more genes involved in blood vessel growth and in protecting cells from conditions of low oxygen called hypoxia than tumors of patients in the other group.

The researchers then looked to see what treatments the individual patients had received, and how they fared.

"The most exciting finding was that those members in the highly vascularized group who had received anti-angiogenic treatment lived significantly longer — on average more than a year more — than others in the same group who did not get anti-angiogenic therapy," said Rubin. "And this analysis was performed using images that already exist as part of the diagnostic procedure for this disease. Our findings speak to the fact that the biology of glioblastoma can vary significantly among individuals, and that certain subgroups of patients may benefit from treatments that appear ineffective when screened across a large unselected mix of patients."

Rubin and his colleagues hope their study will reignite the conversation about the use of anti-angiogenic therapies in glioblastoma, while also enhancing the understanding of the varied biology of the disease.

"This is a turning point."

"This is a turning point," said Rubin. "We believe we can identify those people who are likely to benefit from anti-angiogenic treatments, and also begin to think outside the box to identify other types of therapies for those who are unlikely to respond. This shows that subtyping cancers like glioblastoma can have a huge impact on how we treat disease."

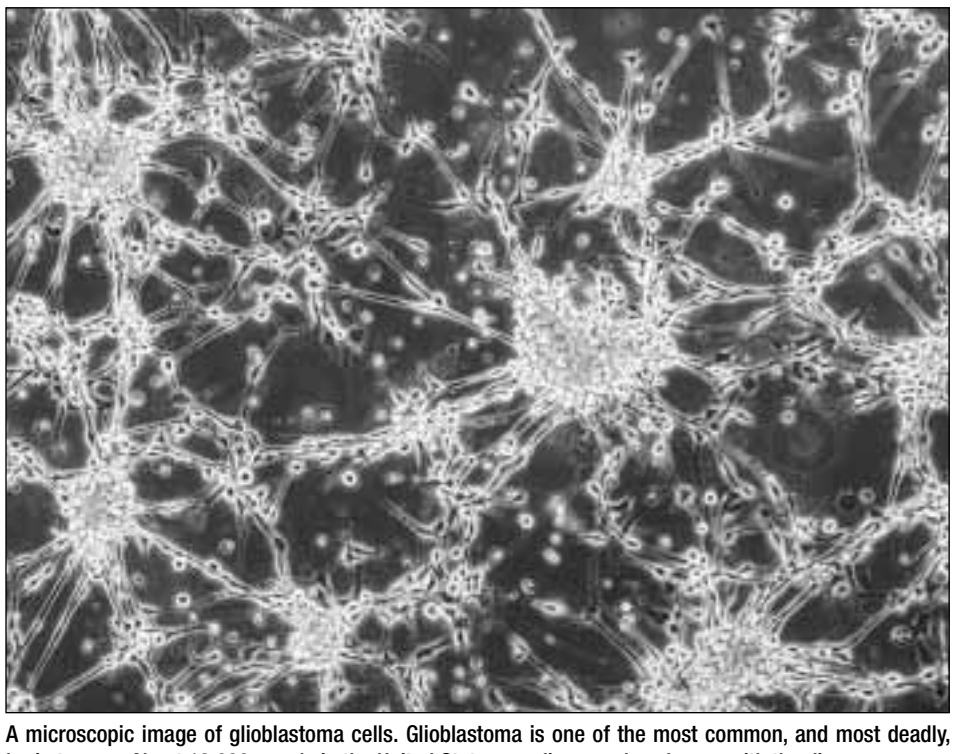
The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors are adjunct clinical instructor Lex Mitchell, MD; former medical student Scott Rodriguez, MD; medical student Abdullah Feroze; clinical assistant professor of radiology Michael Iv, MD; clinical instructor of radiology Christine Kim, MD; clinical assistant professor of neurosurgery Navjot Chaudhary, MD; assistant professor of medicine and of biomedical data sciences Olivier Gevaert, PhD; professor of neurosurgery Griffith Harsh, MD; and professor of neurosurgery Steven Chang, MD.

The research was supported by the National Institutes of Health.

Stanford's departments of Biomedical Data Science, of Radiology and of Medicine also supported the work. **ISM**

ANNA DURINIKOVA / SHUTTERSTOCK.COM



A microscopic image of glioblastoma cells. Glioblastoma is one of the most common, and most deadly, brain tumors. About 12,000 people in the United States are diagnosed each year with the disease.

$26.4 million awarded to researchers for physical activity study

By Tracie White

Stanford researchers have been awarded two grants totaling $26.4 million as part of the largest program ever funded by the National Institutes of Health to study the biological mechanisms of physical activity.

Michael Snyder, MD, professor and chair of genetics, and Stephen Montgomery, PhD, assistant professor of pathology and of genetics, were awarded $15.7 million. They will lead a research team using advanced technological tools to identify and characterize the wide range of molecules that form during or after exercise.

"Our grant is to collect genomic, transcriptomic and epigenomic information and learn about how these relate to the effect of exercise," Snyder said. "We will be determining how exercise affects the body's biochemistry at a detailed level never analyzed previously."

Montgomery added, "A lack of physical activity is a major factor in multiple diseases. This program provides an exciting opportunity to learn the molecular mechanisms underlying physical activity, with the goal of enabling new approaches to improving or maintaining individual health."

A bioinformatics center

A second grant of $10.7 million was awarded to Euan Ashley, DPhil, MRCP, associate professor of cardiovascular medicine and of genetics, to establish and lead a bioinformatics center for data storage available to all the researchers across the NIH program.

Michael Snyder

Stephen Montgomery

Euan Ashley

"The role of the bioinformatics center will be data sharing, data integration with other datasets, and novel analytics," Ashley said.

The NIH program, called Molecular Transducers of Physical Activity in Humans, will award a total of $170 million to researchers across the United States over the next six years to study the molecular changes that occur during and after exercise, with the goal of advancing the understanding of how physical activity improves and preserves health.

"The development of a so-called molecular map of circulating signals produced by physical activity will allow us to discover, at a fundamental level, how physical activity affects our health," Francis Collins, MD, PhD, director of the NIH, said in a news release issued by the agency. "This knowledge should allow researchers and doctors to develop individually targeted exercise recommendations and better help those who are unable to exercise."

The program will include seven clinical trial sites across the country and seven chemical analysis sites. Three awards will go to conduct physical activity studies in animal models. The bioinformatics center will disseminate data and tools to the entire research community, and a coordination center will facilitate activities across the consortium, the release said.

"What is so exciting about this program is that there is no more potent therapeutic intervention than exercise," Ashley said. "Regular physical activity reduces the risk of almost every disease you can think of — heart disease, lung disease, cancer, neurological disease, GI disease, bone disease, back pain, depression. And yet, we have no idea how exercise achieves this magical effect." **ISM**

Heart

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researchers said.

"The ultimate goals of the MyHeart Counts study are to provide real-world evidence of both the physical activity patterns most beneficial to people and the most effective behavioral motivation approaches to promote healthy activity," said Michael McConnell, MD, a professor of cardiovascular medicine at Stanford who is currently on leave while serving as head of cardiovascular health innovations at Verily Life Sciences. McConnell and Anna Shcherbina, a graduate student in bioinformatics, are co-lead authors of the study.

"Physical activity can reduce the risk of heart disease by 50 percent," Ashley said. "We are all working to find ways to help our patients be healthier by encouraging healthy behaviors."

Accuracy vs. estimates

Researchers have already established the importance of physical activity, fitness, sleep and diet in maintaining cardiovascular health, the study noted. Low fitness levels, in particular, are a key risk factor for heart disease, with previous research indicating that insufficient physical activity accounts for 5.3 million deaths per year worldwide.

But in most of the prior clinical studies, researchers have relied on participants to estimate the time spent on physical activity in the preceding days. And people have been consistently shown to overestimate their activity levels, the study noted.

"Traditional research on physical activity and cardiovascular health has been based on people writing down what they remembered doing," McConnell said. "Mobile devices let us measure more directly people's activity patterns throughout the day."

Users who consented to participate in the MyHeart Counts study were asked to keep their phone with them as much as possible. They were also asked to provide some basic health information — such as age, weight, blood pressure, cholesterol levels and risk factors — all of which was kept confidential. This enabled the app to provide participants with feedback on their chances of developing heart disease.

Participants were also asked to complete occasional surveys on such topics as diet, well-being, risk perception, work-related and leisure-time physical activity, sleep and cardiovascular health status.

"The large numbers of subjects we were able to get so quickly provided very rich data sets of information," said Shcherbina, an expert in data analysis, who added that one of the limitations of the study was the disproportionate number of men in their 30s who participated, reflecting the demographics of typical smartphone users.

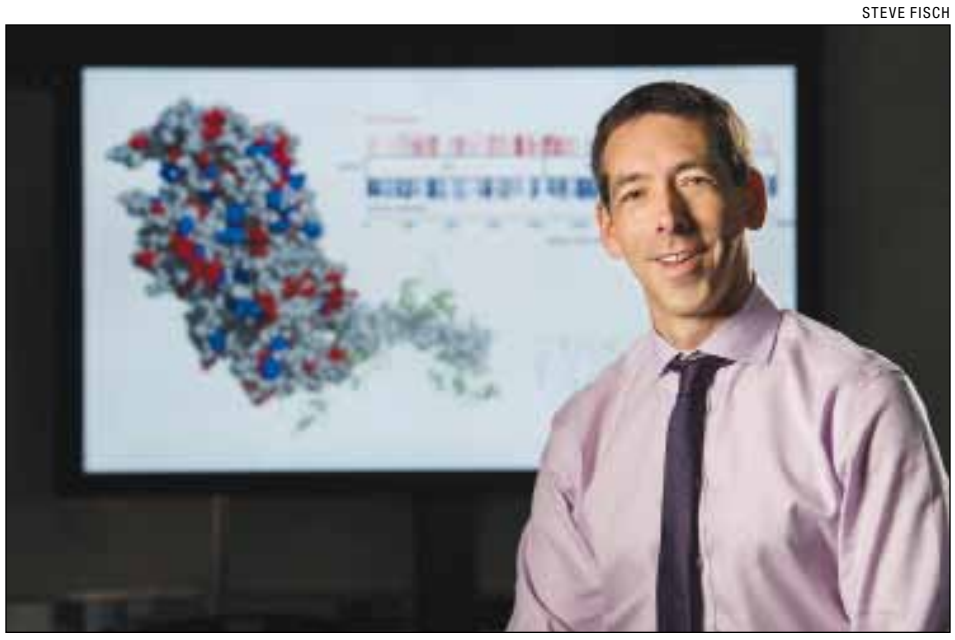
'When' and 'what' matters

"One of the most interesting things we found was that not just the amount of activity mattered but also the pattern," Shcherbina said. "We looked at activity states and compared, say, one person who worked out just at the end of the work day with another person who was active in short bursts throughout the day, changing from sitting to standing to walking."

Results showed that among groups of subjects with similar activity levels, those who were active throughout the day rather than in a single, relatively short interval reported better levels of cardiovascular health with lower rates of chest pain, heart attacks and atrial fibrillation.

This aligns with prior findings that link prolonged periods of uninterrupted, sedentary time with increased risk for metabolic syndrome and diabetes, the study said.

STEVE FISCH



Euan Ashley is the senior author of a paper that found that data collected through MyHeart Counts demonstrates the potential of smartphones to transform the measurement of physical activity and fitness for clinical research.

Results also confirmed what was already generally known: that participants were not accurate at estimating their actual activity levels, she said.

Other notable findings regarding activity patterns indicated that "weekend warriors," those who got most of their exercise on the weekend, were among the healthier groups. And, in relation to sleep, the old adage "early to bed, early to rise" was found to be true, with participants with that type of sleep pattern reporting higher levels of well-being.

Researchers are working on an Android version of the MyHeart Counts app to broaden the reach of the ongoing study, as well as an updated version of the app that will include more motivational feedback to the users about how to improve their heart health.

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.

Other Stanford authors are Aleksandra Pavlovic, MyHeart Counts project manager; graduate students Julian Homburger and Rachel Goldfeder; Daryl Waggott, bioinformatics statistician; Mildred Cho, PhD, professor of pediatrics; Mary Rosenberger, PhD, exercise scientist; William Haskell, PhD, professor emeritus of medicine; Jonathan Myers, PhD, clinical professor of medicine; Mary Ann Champagne, clinical nurse specialist; Emmanuel Mignot, MD, PhD, professor of psychiatry and behavioral sciences; Robert Harrington, MD, professor anc chair of medicine; and Alan Yeung, MD, professor of cardiovascular medicine.

The researchers received software development support from Apple Inc.

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

Coaching module among upgrades to MyHeart Counts app

By Jennie Dusheck

Resolved to improve your heart health in the new year? A newly updated app could keep you on track.

Researchers at the School of Medicine have launched MyHeart Counts 2.0, a major update to the popular research app that allows users to share heart health and activity data with researchers. The upgrades include the Stanford Coaching Module, which will test a series of four health interventions — prompts and suggestions aimed at improving heart health; more user feedback; graphics showing user data; and an improved user interface.

"I'm excited to be able to deliver more data back to the patient," said Euan Ashley, DPhil, MRCP, an associate professor of cardiovascular medicine and of genetics at Stanford and the principal investigator on the MyHeart Counts team. Ashley's team is also aggregating and analyzing heart health data from app users and using it to improve methods of preventing heart disease.

MyHeart Counts 2.0 is the result of Stanford's collaboration with Oxford University and co-developer LifeMap Solutions, a digital health company.

The original MyHeart Counts, launched in the spring of 2015 on Apple's ResearchKit platform, has enrolled more than 54,000 participants — more users than any other ResearchKit app.

The research app allows willing participants to share measures of day-to-day activity levels, cardiovascular health, blood pressure and cholesterol levels with medical researchers at Stanford. A consent module also allows participants who have a 23andMe account to share their genetic information securely with Stanford researchers.

MyHeart Counts 2.0 will present users with graphs that show how they compare to other users in terms of how many steps they take each day, how happy they are, how much they sleep and the quantity of vegetables they are eating. Users will get prompts to learn more about what contributes to heart health.

Among the features of version 2.0 of the MyHeart Counts app are graphs showing how a user compares to others in terms of steps taken each day, amount of sleep and happiness.

Coaching

MyHeart Counts 2.0 features the Stanford Coaching Module, designed in collaboration with Abby King, PhD, professor of medicine and of health research and policy. "We know when it comes to changing key health habits, such as physical activity and daily sitting time, one size definitely does not fit all. Yet, until the advent of mobile apps and other e-health programs, we've had few options for customizing messages and feedback to individuals in real time," she said.

The coaching module will guide participants through a week of baseline measurements, followed by four one-week behavior-change interventions. One intervention, for example, suggests that sedentary participants take a moment to stand up or find ways to increase their daily step count, with the aim of helping them become more active. Participants are randomized into each of the interventions, so the coaching module can act as a randomized trial that will show which interventions are most effective.

The new version of MyHeart Counts "lets us begin to customize feedback to users, and also discover which types of information might be most useful or motivating for different groups," said King.

The app won't look very different in the first, baseline, week, said LifeMap Solutions CEO Corey Bridges. But in the second week, the new features "really come to life. They engage you and become your personal health coach," he said.

"The most unique thing about the new version is its ability to randomize patients and intervene," said Ashley. For example, depending on which week of the four-week intervention you're in, the app might notice you've only taken 2,000 steps and suggest that you plan a walk later in the day.

Such randomized interventions, said Ashley, will give researchers a handle on whether a particular intervention for an individual is prompting a change in behavior for the better. Ultimately, he said, future versions of MyHeart Counts will make it easy for participants to see and analyze their own data.

The app 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.

A secure platform

Inspired by apps like MyHeart Counts, many Stanford faculty are now building apps of their own. In response, Stanford Medicine has created a HIPAA-compliant platform to store data from research applications built on smartphones.

MyHeart Counts 2.0 can be downloaded from Apple's App Store.

For more information about MyHeart Counts, go to http://myheartcounts.stanford.edu. ISM

Gene activity predicts progression of autoimmune disease

By Jennie Dusheck

Researchers at the School of Medicine and six other institutions have designed a new diagnostic tool for a rare and deadly autoimmune disease that affects the skin and internal organs.

By measuring the activity of genes in tiny skin samples, the researchers were able to predict disease progression in patients as much as a year earlier than clinicians who used standard methods for evaluating patients.

The study was published Dec. 22 in *JCI Insight*. The lead authors are Shane Lofgren, a research associate at Stanford, and Monique Hinchcliff, MD, associate professor of medicine at Northwestern University. The senior author is Purvesh Khatri, PhD, assistant professor of medicine at Stanford.

Systemic sclerosis, also called scleroderma, is an autoimmune disease that causes scarlike thickening of the skin and internal organs, such as the kidneys and lungs. According to Hinchcliff, systemic sclerosis affects about 100,000 people in the United States.

A better test

The cause of systemic sclerosis is unknown, and there are no drugs approved by the Food and Drug Administration for treating it. Many patients are given drugs that are approved for use in other diseases, but each drug is clinically effective in only a fraction of patients.

To find out if a patient is responding to treatment, clinicians use a test called the modified Rodnan skin score, in which a doctor pinches the skin to see how thick it is. For the test, the physician squeezes the patient's skin in 17 places, rating the thickness of each pinch of skin on a scale of 0 to 3 and adding the scores together for a maximum score of 51.

"It's a very crude measure," Khatri said. He noted that despite careful training, doctors may give the same patient different scores, depending, for example, on the patient's body-mass index.

Different physicians evaluating the same patients may agree only 60 to 70 percent of the time, Hinchcliff said. "It has always embarrassed me to pinch a patient's skin in 17 areas to try and accurately assess the degree of skin fibrosis. In this day and age, it would seem we should be more precise," she said.

Because the measures of disease progression are imprecise, said Khatri, it can take two years for physicians to be sure if a given treatment is having any effect. A more precise measure of disease progression has long been needed.

The team used publicly available patient data shared by hospitals across the United States to search for a set of genes whose activity would mark the progression of systemic sclerosis, or SSc.

Gene expression is the process by which cells extract information from genes and render it as molecules of protein or RNA. Cells have the capacity to express more or less of each molecule, creating a pattern of expression that changes according to the presence of infections or of autoimmune diseases such as SSc. Khatri and his team identified 415 genes whose expression changed in a pattern that indicated how serious a person's SSc had become. The researchers were able to use these gene-expression patterns as the basis for a test, which they called the SSc Skin Severity Score, or 4S. They used SSc patient data from two clinical centers to identify the 415 genes, and data sets from patients from five additional centers to validate the new test. They also included data from healthy participants who served as controls.

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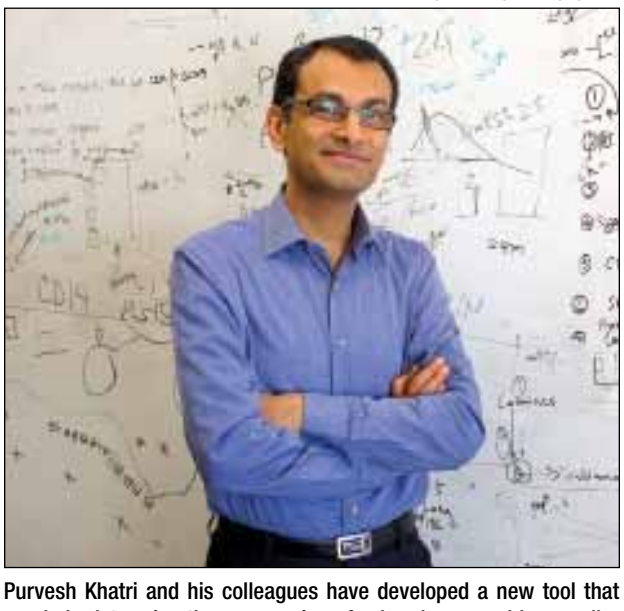

Purvesh Khatri and his colleagues have developed a new tool that can help determine the progression of scleroderma and how well a patient is responding to treatment.

It was easy to distinguish the gene-expression data related to healthy skin samples from the data for diseased skin samples, said Khatri. "The data for all the healthy skin fell within one bubble," he said, "while all the data for the scleroderma patients fell within another."

Getting results a year earlier

The team looked at data from a cohort of Northwestern University patients who had been tested repeatedly with the skin pinch test while being treated with a drug. The 4S test — applied to this preexisting set of patient data — could distinguish patients who were improving from those who were not 12 months after their treatment began. In contrast, the doctors' skin pinch test from the same set of data took 24 months to identify which patients were improving.

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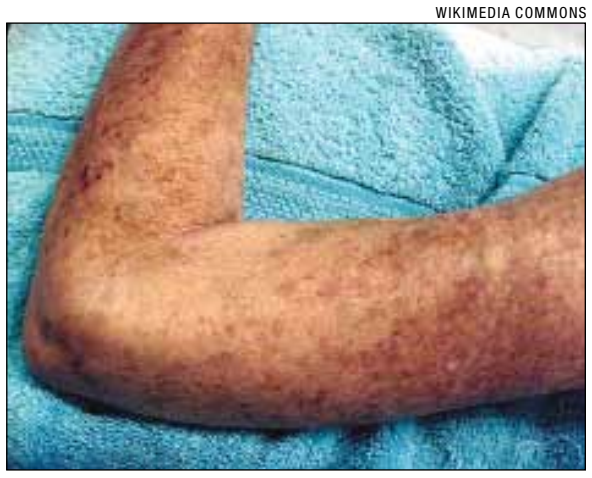


Scleroderma is an autoimmune disease that causes scarlike thickening of the skin and internal organs. It can cause skin lesions like those pictured above.

"In the data from Northwestern, all the patients were getting exactly the same treatment, the same drug," said Shane. "Yet we were able to predict a year before the clinician which patients were getting better and which were getting worse."

> **"We could predict on an individual level which patients would get better or worse."**

Clinical trials, as opposed to retrospective studies looking at pre-existing data, are needed to validate the 4S test, the researchers said. But if it works as well as Khatri and his collaborators hope, clinicians may be able to evaluate patients' response to treatments much more quickly, so they can be switched to some other treatment that may work. The test could also help advance the search for better therapies.

"And what was really cool was that we could predict on an individual level which patients would get better or worse," Khatri said.

The 4S test 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.

A possible treatment?

The study also uncovered a gene-activity signal suggesting the involvement of epidermal growth factor receptors in the disease, a fact that was previously unknown, said Khatri. EGFR is important in cell division and plays a role in cancer and other diseases. In SSc, "we showed that EGFR is consistently upregulated," Khatri said. And, he added, drugs that have been approved by the FDA for treating EGFR-related conditions may turn out to be useful in treating patients with systemic sclerosis.

Soon, he added, his team will begin giving EGFR-inhibiting drugs to mice with a sclerodermalike condition to see if it helps.

"It's very exciting," said Khatri. "This is a disease that has stumped people for more than 25 years."

Other Stanford co-authors are professor of dermatology David Fiorentino, MD, PhD; professor of medicine Paul Utz, MD; associate professor of medicine Lorinda Chung, MD; postdoctoral scholars Peggie Cheung, PhD, and Alex Kuo, PhD; and rheumatology fellow Antonia Valenzuela, MD.

In addition to Northwestern, researchers at the following institutions also contributed to the study: Dartmouth College, the University of California-San Francisco, the Hospital for Special Surgery, the University of Texas Health Science Center and the Veterans Affairs Palo Alto Health Care System.

The research was supported by the National Institutes of Health, the Bill and Melinda Gates Foundation and the Scleroderma Research Foundation.

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

Starfish larvae create complex water whorls to eat and run

By Tom Abate

Peek into a tide pool and you may see a starfish clinging firmly to a rock. But its secure adulthood comes at the expense of a harrowing larval journey.

Tiny starfish larvae — each smaller than a grain of rice — spend 60 days and 60 nights paddling the open ocean, feeding to accumulate the energy needed to metamorphose into the familiar star shape.

Now, a team of Stanford scientists has revealed the beautiful and efficient mechanism that allows these humble creatures to survive to adulthood.

The findings are described in a paper published Dec. 19 in *Nature Physics*. Manu Prakash, PhD, assistant professor of bioengineering, is the senior author. The lead author is graduate student William Gilpin.

"We have shown that nature equips these larvae to stir the water in such a way as to create vortices that serve two evolutionary purposes: moving the organisms along while simultaneously bringing food close enough to grab," Prakash said. Using experimental techniques that capture the visual beauty and mathematical underpinnings of this mechanism, the researchers show how the shape and form of starfish larvae enable the functions that are necessary to support life.

"When we see strange and beautiful shapes in nature we bring them back to the lab and ask why they evolved this way," Prakash said. "That is the perspective we bring to biology: to understand mathematically how physics shapes life."

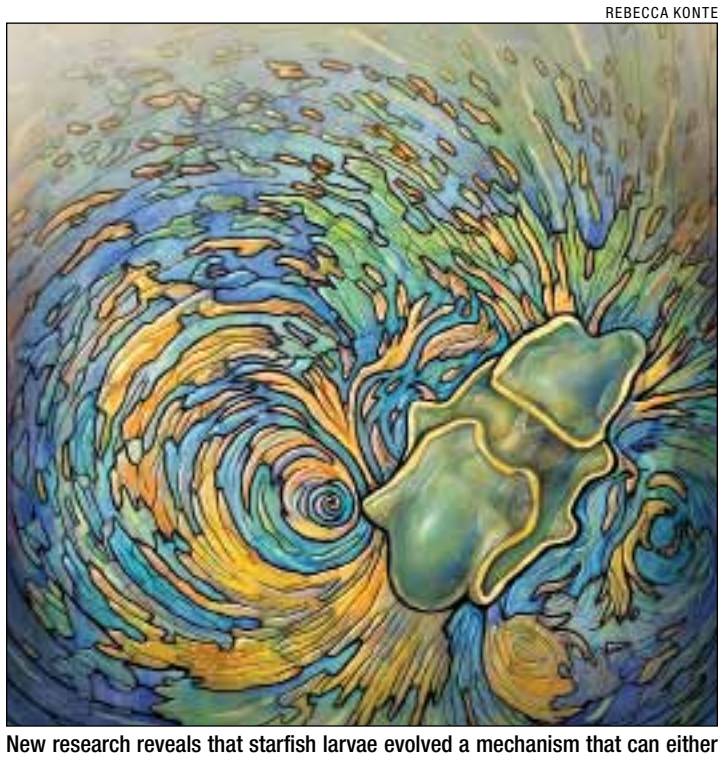
Gilpin said these findings shed light on similar evolutionary challenges involving dozens of marine invertebrates that are related to starfish larvae in a key way.

"Evolution seeks to satisfy basic constraints," Gilpin said. "The first solution that works very often wins."

These experiments began in the summer of 2015 at Stanford's Hopkins Marine Station in Pacific Grove, California. The researchers were taking a course on embryology when they began to wonder about the evolutionary underpinnings of the starfish larva's shape. Why did it end up looking as it did? Bringing their curiosity back to the Prakash lab, the group studied the organisms in a systematic way, feeding the larvae nutrient algae and observing their movements with video-enabled microscopes.

"Our first eureka moment came when we saw the complex vortices **See STARFISH, page 6**

REBECCA KONTE



New research reveals that starfish larvae evolved a mechanism that can either stir the water to bring food closer or propel the organism toward better feeding grounds.

Cancer

continued from page 1

Sanjiv Gambhir

CTCs from the blood sample and allows the rest of the blood to flow through the sifter. The CTCs pulled from the blood are then deposited into a flat array of tiny wells, each large enough for only one cell. Now the tumor cells are ready for genetic analysis. Each flat of 25,600 wells looks like a miniature muffin tin, with room for a lot of tiny muffins.

The new technique serves as a proof of concept for collecting and analyzing lung cancer cells from blood samples. If the technique receives approval from the Food and Drug Administration, it could be used to tell how cancer cells have evolved in response to chemotherapy and which drug is the best to use next in individual patients.

In principle, the technique should work just as well with other kinds of cancers, Wong said. "We validated our device on lung cancer because of the difficulties of doing lung biopsies," he said. "But the technology is not limited to profiling lung cancer. We could swap out markers and adapt the technique to other types of cancers."

Cost of less than $30

The approach that the team developed could be used to look at mutations in three or four genes, and it requires no more than 2 milliliters of blood — about half a teaspoon. The test can be completed in about five hours, the researcher said, and costs less than $30. By comparison, a single state-of-the art biopsy of lung tissue with DNA sequencing costs about $18,000 and takes as long as three weeks to furnish results. Johnson & Johnson's CellSearch — another blood test, already approved by the FDA — costs about $900 and takes a week to deliver results.

"We feel that we have solved a lot of the technical hurdles," said Wong. "The blood draw is cheap enough and noninvasive enough that it could be done on a weekly basis throughout treatment."

The team's 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.

Other Stanford co-authors are graduate students David Kurtz, MD, Amin Aalipour and Jacob Chabon; postdoctoral scholar Ophir Vermesh, MD, PhD; research assistants Kelsey Pian and Justin Carter; former research assistant Susie Suh; instructor of radiology Mehran Jamali, MD; clinical research associate Carmen Say; professor of medicine Ware Kuschner, MD; professor of medicine Erich Schwartz, MD; professor of cardiothoracic surgery Joseph Shrager, MD; assistant professor of medicine Joel Neal, MD, PhD; associate professor of medicine Heather Wakelee, MD; and assistant professor of radiation oncology Maximilian Diehn, MD, PhD.

This research was supported by the National Institutes of Health, the Canary Foundation, and the LUNGevity Foundation.

Stanford's Department of Medicine also supported the work.

Stanford University has filed for patents on the technology used in connection with this work. ISM

Epilepsy

continued from page 1

online Dec. 15 in *Neuron*, point to the possibility of improved ways of reducing, halting or possibly even preventing absence seizures in susceptible children. There's reason to think these findings may also apply to a wider range of generalized seizure types, including the more dramatic and better-known grand mal, characterized by involuntary jerking movements in addition to loss of consciousness.

Huguenard shares senior authorship of the study with Jeanne Paz, PhD, a former postdoctoral scholar in his group and now assistant professor of neurology at the University of California-San Francisco and assistant investigator at the Gladstone Institutes in San Francisco. After Paz, who initiated the study, departed for UCSF, the experiments were continued by Stanford graduate student Jordan Sorokin, the study's lead author, under Huguenard's direction.

Multiple daily seizures

"Many people think of absence seizures as being mild because there's no shaking or falling on the floor," said Paz. "But some kids have more than 200 absence seizures a day, making it impossible for them to learn at school. And the drugs they take for their seizures may not work well."

Absence seizures are a type of so-called generalized seizures: patterns of rhythmic nerve-cell firing activity that, while originating in one or another brain region, propagate throughout the entire organ. Implicated in all generalized seizures is nerve circuitry in a deep-brain structure called the thalamus, whose functions include relaying sensory information to the cerebral cortex via a nerve projection called the thalamocortical tract.

Resorting to an increasingly widespread technology called optogenetics, pioneered in the lab of study co-author Karl Deisseroth, MD, PhD, a Stanford professor of bioengineering and of psychiatry and behavioral sciences, the researchers inserted the gene for a light-sensitive cell-surface protein called an opsin into a set of excitatory nerve cells in the thalamocortical tract of rats and mice bred to be prone to absence seizures.

As a result of this manipulation, the opsin appeared on the surfaces of those excitatory thalamocortical nerve cells. The particular opsin the scientists used for some of their experiments was inhibitory. Its presence on nerve cells meant that whenever yellow light was delivered to them via an implanted fiber-optic cable, those cells would be prevented from firing.

The thalamocortical tract's excitatory nerve cells are somewhat like excitable second-graders. Imagine a classroom filled with children who share an inability to stay completely quiet for more than five seconds. Imagine, further, a teacher who doesn't mind the occasional loud whisper or random outburst but who will not abide noise above a certain threshold. When the din exceeds that level, the teacher shouts a show-stopping, "Quiet!"

The inevitable result of this enforced silencing: Five seconds later, the room will erupt in a burst of noise, in turn inducing an authoritarian cease-and-desist command, followed by another eruption, and so forth. The very act of inhibition drives a pattern of rhythmic firing.

Disrupting the pattern

Similarly, back in the thalamus, inhibition (the "teacher" analog) is meted out to the thalamocortical tract's excitatory nerve cells by a different set of cells in the thalamus whose job it is to generate useful rhythms in this brain structure. A gentle, rhythmic firing pattern in the thalamocortical tract is typical during normal sleep. It makes sense, when an individual needs sleep, to tune out disruptive sensory inputs from the thalamus to the cortex.

John Huguenard

But in absence epilepsy, this useful, rhythmic thalamocortical lullaby is hijacked and amplified into the distortion range. It appears that subtle defects within the circuitry can predispose the thalamocortical tract's firing to slip too easily into lockstep synchrony.

The researchers had observed that firing in the thalamocortical tract shifted from a chaotic to a rhythmic pattern during their test animals' naturally occurring seizures. Using optogenetics, the scientists were able to abruptly inhibit firing in excitatory thalamocortical cells — and, by so doing, to induce seizures at will in the animals — at the flick of a switch.

"A single pulse of yellow light was enough to generate rhythmic firing activity throughout the cortex, in both hemispheres of the brain," Huguenard said.

The insertion of a different kind of opsin, also developed in Deisseroth's lab, far from inhibiting excitatory thalamocortical cells made them more excitable in response to a blue-light pulse. This predisposition could be canceled by administering yellow light. Toggling from one to another color of delivered light, the investigators demonstrated that making the excitatory thalamocortical cells less susceptible to inhibition disrupted their collective firing synchrony and blocked seizure activity.

"Our study shows that the thalamus is a choke point whose involvement is essential to the maintenance of absence seizures," Paz said. Both Paz and Huguenard suggested that treatments capable of guiding excitatory thalamocortical nerve cells from a tightly synchronized to a more chaotic firing pattern may be able to halt absence seizures — and, maybe, other forms of generalized epilepsy, too.

Other Stanford co-authors of the study are former postdoctoral scholars Eric Frechette, MD, PhD, and Matthew Abramian, PhD, who is now a clinical trials research coordinator at Stanford.

The study was funded by the National Institute of Neurological Disorders and Stroke, the Stanford Neuroscience Graduate Program and Citizens United for Research in Epilepsy.

Stanford's Department of Neurology and Neurological Sciences also supported the work. ISM

Starfish

continued from page 5

flowing around these animals," said Vivek Prakash, PhD, a co-author of the study and postdoctoral scholar in bioengineering (no relation to the senior author). "This was beautiful, unexpected and got all of us hooked. We wanted to find out how and why these animals made these complex flows."

Manu Prakash

Gilpin said the vortices were puzzling because they seemed to make no evolutionary sense. It took a lot of energy to create spiral flows of water; thus, a larva with just three imperatives — feed, move and grow — had to have a reason to expend such effort.

Orchestra of eyelashes

Once the researchers figured out how the larvae made the water swirl, that understanding led them to the why, and the experiment zeroed in on one of evolution's most prevalent structures: the cilia, from the Latin word for eyelashes.

Imagine that the cilia on a starfish larva are like the oars that might be used to row an ancient galley, except that each larva has about 100,000 oars, arranged in what researchers call ciliary bands that gird the organism in a pattern far more complex than any galley's oars.

The rowing metaphor hints at the complexity the researchers found as they studied how these 100,000 eyelashes paddled the larva through water.

Like oars, the cilia had three potential actions: forward, reverse and stop. And just as with oars, the cilia moved in different synchronized patterns to create different motions. Presumably orchestrated by its nervous system, the larva beats its 100,000 eyelashes in certain patterns when it wants to feed, so as to swirl the water in a way that brings algae close enough to grab. Then, with a different flutter of eyelashes, the larva creates a new pattern of whorls and speeds off.

The researchers realized that they were observing an active and previously unknown mechanism that improved the larva's odds of survival. The physical structure of the starfish larva, controlled by its nerves, allows it to make feed-versus-speed trade-offs — lingering whenever algae are plentiful, then darting off should nutrients grow scarce.

As they considered the implications of these findings, the researchers hypothesized that this feed-versus-speed mechanism likely applied to other invertebrate larvae that, though different than starfish larvae in form, are nonetheless known to have similar ciliary bands. In future experiments, the researchers plan to use the same techniques to study these other larval shapes. What they hope to learn is how evolution has taken a certain mechanism, the ciliary band, and solved the same feed-versus-speed trade-off in dozens of different forms and shapes.

"That's what we do in my lab: look for fundamental principles that we can express in equations to describe the beauty, diversity and functions of different forms of life," Prakash said.

Prakash is a member of Stanford Bio-X and Stanford ChEM-H, and he's an affiliate of the Stanford Woods Institute for the Environment.

The work was supported by the U.S. Army Research Laboratory's Multidisciplinary University Research Initiative and the National Science Foundation.

Stanford's Department of Bioengineering, which is jointly operated by the School of Medicine and the School of Engineering, also supported the work. ISM

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Infectious disease researcher on bread-baking

Making bread is an art, science and passion project for Fiona Strouts, PhD, a research scientist in infectious diseases at the School of Medicine.

Her baking began as a hobby several years ago, but now Strouts operates a business, L'atelier du Pain, and sells her whole-grain bread at the Portola Valley Farmers Market. Recently, Jennifer Huber, a frequent contributor to the school's blog, Scope, caught up with her by email.

1 How did you start baking bread?

STROUTS: I learned to make bread about eight years ago from my Italian housemate when I lived in London during graduate school. She taught me to make 100 percent whole-wheat sourdough bread that we would bake together on the weekends. The bread was fairly dense, and provided good fuel for cycling.

I now make whole-grain, naturally leavened breads using mostly California-grown wheat. The favorite seems to be the Sprouted Lentil & Rye bread. But my personal favorite for everyday eating is the Sonora Field Blend; it has great flavor and aroma. Sonora wheat was one of the first varieties planted in California in the early 1800s.

2 I've heard that you grind your own wheat. Why?

STROUTS: Yes, I stone-grind my own wheat because I want to capture the flavor and nutrients, which come mostly from the germ and bran portions of the wheat berry. I buy bags of wheat berries directly from farmers, and then mill them into flour right before I mix the dough. Milling the wheat myself also ensures that the flour is 100 percent whole grain. Wheat is very nutrient-dense compared with other grains, but only when it is in the truly whole-grain form — nothing added and nothing removed from the original wheat grain.

3 Why did you decide to turn your hobby into a business?

STROUTS: A number of things inspired me, and they all came together a few months ago. I grew up in France, and in the village where my parents live there was a local baker and friend. The highlight of the week was going to the market on Saturday and then stopping by his house to pick up bread. There would be others from the village there, and we'd share a savory pastry and a glass of wine before picking up the bread and going home for lunch. I miss that sense of community, and I wanted to recreate something similar.

Then, almost a year ago, I started learning more about all of the farmers in California who are passionate about sustainable agriculture and who are growing different varieties of wheat — both ancient and modern. I loved discovering the different flavors and properties of these wheats for bread making.

In addition, I've always been very interested in health and population health. Making whole-grain, naturally leavened breads is a way to provide a healthy option for people.

4 How do you juggle baking, running a business and doing research?

STROUTS: Good question! It takes organization and prioritization. I used to bike race, and the training required a lot of discipline. But starting the business was less structured, and it took longer than I thought it would, as I was doing it in my spare time. I spent several weekends practicing baking large batches of bread and sharing it with some of my labmates, which I think they appreciated. The market is one day per week, and it's a manageable scale for one person. I've reduced my full-time equivalent [work] hours accordingly to be able to do both, and my adviser has been very supportive.

5 Explain your research at Stanford. Has it given you any insights into bread-making?

STROUTS: I work in the lab of David Relman, MD, on a project focused on improving the diagnosis and prognosis of systemic infections in humans, using sequencing of both microbial nucleic acids and host transcripts derived from blood. I am trying to understand what those blood profiles look like during states of health. And whether we're able to detect the presence of bacteria in the blood of healthy people, to help interpret what we see in sick individuals with suspected infections.

My background has helped me understand sourdough-bread making from the aspect of microbial fermentation and the effects of time and temperature. I've actually become quite a keen home fermenter. I have various other projects going — including yogurt, kefir, kombucha [a fermented tea drink], shoyu [soy sauce] and miso — for which I converted the dishwasher into a fermentation chamber with a little space heater. Both baking and cooking are science, so it has also helped more generally in figuring out the properties of different types of wheat. ISM

MICHELLE LE / EMBARCADERO MEDIA

Fiona Strouts began baking bread as a hobby several years ago, but now she operates a business, L'atelier du Pain, and sells her whole-grain bread at the Portola Valley Farmers Market.

David Chan on the 'black box' of rising costs, inconsistent care

By Krysten Crawford

Few people understand the high costs of medical services in the United States better than David Chan, MD, PhD, a practicing physician and economist specializing in health care. But even Chan isn't immune from sticker shock at the doctor's office.

On a visit last year to his doctor, Chan, a Stanford assistant professor of medicine, underwent a routine test for seasonal allergies. He figured it would cost about $500. The actual charge was closer to $5,000.

"I should be one of health care's most informed customers," said Chan. "But like most people, I didn't think to ask the price for the test, and my doctor probably didn't know it, anyway."

To Chan, who is also a faculty fellow at the Stanford Institute for Economic Policy Research, the experience illustrates what's hobbling U.S. health care. Although much research into health economics has focused on issues related to insurance, the delivery of patient care — specifically, how to lower costs and manage quality at the ground level — "is really where health care becomes a black box," he said. Economists haven't figured out why costs and patient outcomes vary widely, even from one hospital to the next in the same city.

The key to opening that box, Chan said, is to better understand human behavior in health care. This includes factors that make it easier or harder for doctors, nurses and other health care workers to do their jobs cost-effectively day in and day out.

Through his research into health worker productivity, Chan is revealing groundbreaking insights. Several of his studies, for example, have examined how emergency rooms are staffed. In one, published last summer in the *Journal of Political Economy*, Chan showed that the typical practice of relying on triage nurses to assign patients to emergency room doctors is far less effective than doctor-managed assignments.

David Chan

In a 2015 National Bureau of Economic Research working paper, Chan found that ER doctors are far more likely to order tests, which can be done quickly but often at a high price, at the end of their shifts. They do this because, like most workers, they want to clock out on time.

Beyond the ER, Chan recently completed a study that suggests obstetricians are more likely to perform C-sections when caring for patients they know, particularly when their own patients have had complications. In another study, he's analyzing whether physicians or machines make better treatment decisions.

He's also midway through a five-year, $1.25 million National Institutes of Health study that looks at whether doctors eventually tune out electronic reminders that alert them, say, to write a prescription refill or schedule a test for a patient.

Labor and organizational economics factor heavily in Chan's research. "There are parallels across cement or airline-catering companies," Chan said. "Health care is just an example of a broader phenomenon of big differences in productivity in our economy."

Changing direction

When Chan entered UCLA's School of Medicine — in 1999, shortly after earning a bachelor's degree in mathematics and economics from the University of California-Riverside — he expected to follow in his father's footsteps and practice medicine full time. But a course he took on health policy in his second year changed everything.

"I realized I was much more interested in the big economic and policy questions surrounding health care than I was in studying psychology or anatomy," said Chan, who is also a core faculty member at Stanford Health Policy.

It wasn't such a surprising shift. He had planned to practice internal medicine, which is a specialty that attracts an economist-like mindset. "Internists want to understand processes and what ties everything together," he said.

Chan took a hiatus from medical school and went to England, where he earned a master's degree in health policy, with distinction, from the London School of Economics. A year later, in 2003, Chan graduated with a master's degree in economics for development from the University of Oxford.

By then, Chan was sold on a career in academia as a health policy expert. He returned to UCLA to finish his medical degree in 2005 and then completed his residency at Brigham and Women's Hospital in Boston, where he had a front-row seat in Massachusetts' rollout of universal health care. Chan went on to earn a PhD in economics from the Massachusetts Institute of Technology in 2013.

While at Brigham and Women's, Chan received a three-year Harvard Medical School Faculty Development Fellowship and taught at Harvard Medical School. He also received fellowships with the Food and Drug Administration and, in 2011, spent a year as the entrepreneur in residence at the White House Office of Science and Technology Policy.

Chan joined Stanford's faculty shortly after graduating from MIT. That same year he signed on as an investigator with the Veteran Affairs Palo Alto Health Care System, where he now treats military veterans for four weeks every year.

Drawing a distinction

Chan's firsthand experiences as a practicing physician inform his views of the challenges facing U.S. health care. "As a doctor, you realize that a lot of what drives what you do is not related to the patient in front of you," he said. At Brigham and Women's, for instance, he learned that surgeons and internists could have conflicting motives — similar to how different teams of workers in other businesses sometimes clash.

But the analogy, Chan said, between behavior and productivity in health care versus other workplaces isn't perfect. The problems facing health care are compounded by the acute lack of information sharing. His visit to his primary care doctor for allergy treatment was a stark reminder of that.

"There are all of these barriers to information sharing in health care," he said, "and that explains a lot in terms of the lack of productivity, efficiency and standards."

By peering into health care's granular workings, Chan aims to help open the black box of rising costs and inconsistent care. ISM

Therapy dogs take a bite out of student stress before exams

By Kris Newby

Erin Devine, PhD, a first-year medical student at the School of Medicine, was on her way to study for an anatomy final when she was stopped in her tracks by a pack of dogs.

The animals immediately went to work, dissipating the worries of Devine and other students by making themselves available for hugs and offering up free licks. Therapy dogs, it seems, enjoy their jobs.

"I've always loved playing with dogs. Their affection and kisses are a great way to de-stress and take your mind off studying for a few minutes," said Devine, as she scratched one of the dogs' necks. The dog, Crosby, licked her face in gratitude.

Beyond the anecdotal reports that say loving dogs make people happy, there's a growing body of evidence that visiting therapy dogs promote emotional and physical health among students. This year, a randomized study out of Virginia Commonwealth University suggested that college-aged students felt significantly less stress after interacting with therapy dogs for just 15 minutes. And for many of the students, this experience brings back happy memories of beloved family dogs.

Margaret Govea, director of medical student wellness, is an enthusiastic supporter of Stanford's therapy dog program, and she works with Martha Kessler, leader of the comfort dog pack, to schedule therapy sessions throughout the year.

Therapy dogs take exams, too, said Kessler, who is also an executive director of finance and administration at the School of Medicine. Her 6-year-old golden retriever, Oliver, undergoes training and testing throughout the year. So far he has passed tests for canine good citizen advanced, beginning novice obedience, companion dog and therapy dog certifications.

She thinks the best therapy dogs are born with heightened qualities of empathy and calmness. Oliver, for example, is part of an accomplished line of comfort dogs: His mother provides Wesleyan students with therapy, his sister visits Yale students during exams and his brother regularly holds sessions at the University of Massachusetts.

After the student therapy session was over, Oliver and Kessler went to the third floor of the Li Ka Shing Center for a short visit with Lloyd Minor, MD, who is a pet parent of two Portuguese water dogs, as well as the dean of the School of Medicine.

"Even medical school deans can benefit from comfort dog therapy," said Kessler. ISM

KRIS NEWBY

A therapy dog helps first-year medical student Erin Devine de-stress on her way to study for a final.

OF NOTE

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

LACRAMIOARA BINTU, PhD, was appointed assistant professor of bioengineering, effective Jan. 1. Her research focuses on understanding the dynamics of gene and chromatin regulation to improve mammalian cell engineering.

THOMAS CHERPES, DVM, MD, was appointed assistant professor of comparative medicine, effective Dec. 1. His research interests include the effect of female hormones on immune responses to genital-tract pathogens, host responses to chlamydia infection and the development of cellular immunotherapies for cancer.

MAXIMILIAN DIEHN, MD, PhD, assistant professor of radiation oncology, was elected to the American Society for Clinical Investigation. He was recognized for his work using sequencing to analyze circulating tumor DNA. The society includes more than 3,000 physician-scientists from all medical specialties who are selected for their significant research accomplishments.

PRASANNA JAGANNATHAN, MD, was appointed assistant professor of medicine, effective Jan. 1. His research focuses on the mechanisms of protective immunity in malaria and on immunogenic therapies and vaccines.

THOMAS ROBINSON, MD, was awarded the 2016 Bloomberg Manulife Prize for the Promotion of Active Health administered by McGill University. The prize, which includes a research award of 50,000 Canadian dollars (about $37,777), recognizes researchers who enhance the understanding of how physical activity, nutrition or psychosocial factors affect health. Robinson, the Irving Schulman, MD, Professor in Child Health and a professor of pediatrics and of medicine, was honored for his work combating childhood obesity.

SUI WANG, PhD, was appointed assistant professor of ophthalmology, effective Jan. 1. Her research focuses on understanding the molecular mechanisms underlying retinal diseases and retinal development by investigating gene regulatory networks.

KATJA WEINACHT, MD, PhD, was appointed assistant professor of pediatrics, effective Oct. 1. Her clinical work focuses on genetic immune diseases and immune dysregulation. Her research examines the relationship between mitochondrial bioenergetics and cell development and explores the use of stem cell therapy for patients with DiGeorge syndrome.

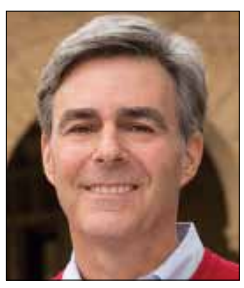
J. BRADLEY ZUCHERO, PhD, was appointed assistant professor of neurosurgery, effective Jan. 1. His research interests include the developmental biology of glia and diseases of the nervous system. ISM

Lacramioara Bintu

Thomas Cherpes

Maximilian Diehn

Prasanna Jagannathan



Thomas Robinson

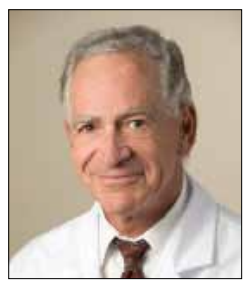
Sui Wang

Katja Weinacht

J. Bradley Zuchero

State stem cell agency awards Strober $6.6 million

Samuel Strober, MD, a professor of medicine, was awarded $6.6 million by the governing board of the California Institute for Regenerative Medicine on Dec. 15 to conduct a phase-1 clinical trial to test a new way of inhibiting the rejection of transplanted kidneys. The award marked the 10th clinical trial funded by the institute in 2016.



Samuel Strober

The clinical trial will test whether injecting blood stem cells and T cells from the kidney donor at the time of transplant will enable the recipient to more readily accept the new organ. The institute called the approach, which would hopefully eliminate the need for ongoing immunosuppressive drug treatment, "deceptively simple" in a blog post about the awards.

About 17,000 kidney transplants are performed in the United States each year. Recipients must undergo a lifetime of anti-rejection drugs, which increase their risks of infection, cancer and heart disease.

Strober's award was one of two approved at the meeting. An additional $8.3 million was awarded to University of California researcher Henry Klassen, MD, PhD, and the biotech company jCyte to continue clinical trials on a treatment for retinitis pigmentosa, a progressive, inherited eye disease that causes blindness in early adulthood. ISM