INSIDE STANFORD MEDICINE

Volume 10, No. 4 ■ February 26, 2018 ■ Published by the Office of Communication & Public Affairs

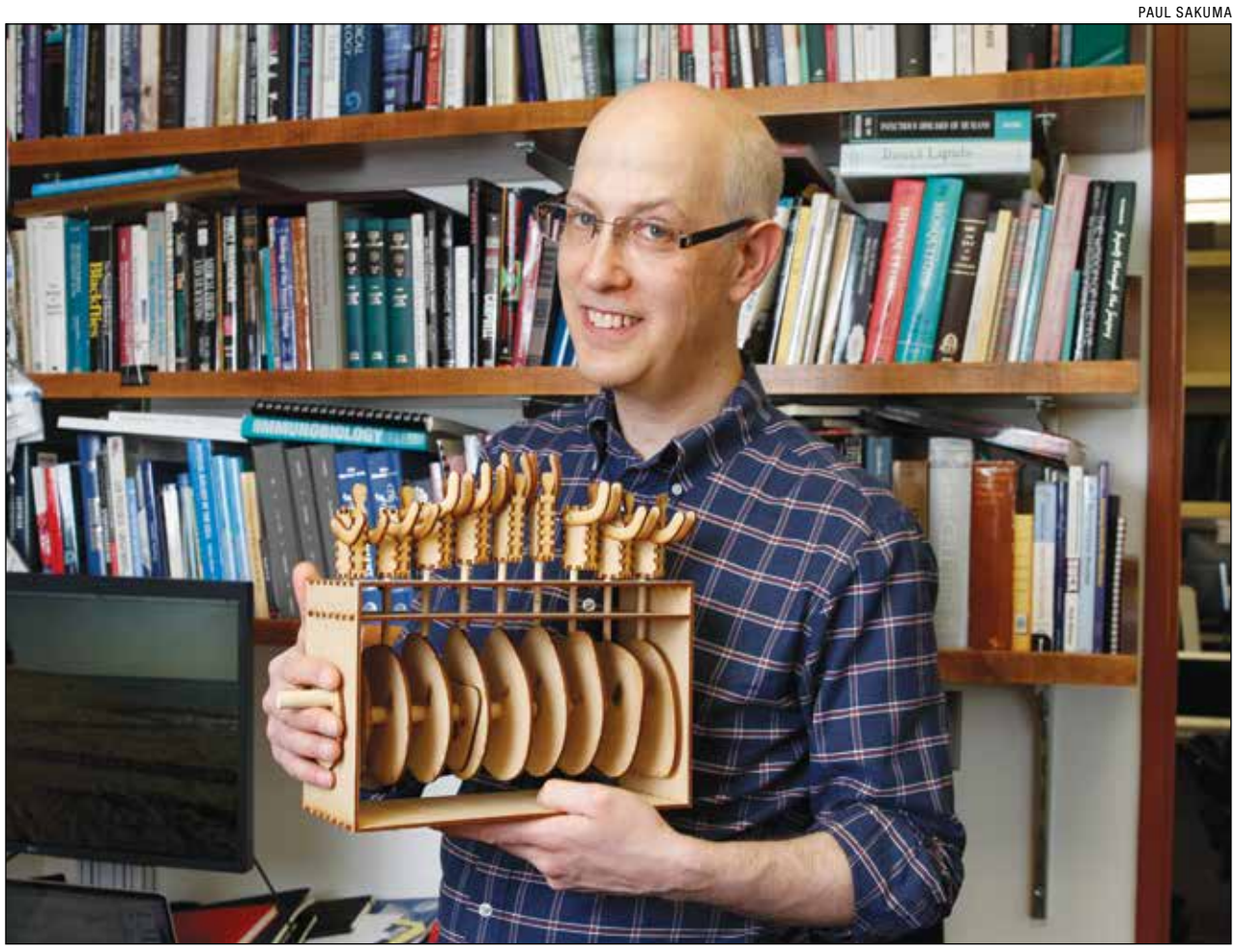
The new issue of *Stanford Medicine* magazine delves into research that pushes boundaries.

Page 5

Data explained with sculptures and gizmos

By Bruce Goldman

PAUL SAKUMA



David Schneider builds kinetic sculptures to help convey data from the sickness and recovery cycles of animals infected by diseases.

On a wall-mounted shelf in the office of David Schneider sit two-dozen or more empty Diet Coke bottles of varying shapes and sizes. They're emblazoned with various languages, testifying to all the places he's downed one of the beverages. He's not a coffee drinker.

There's also a nice bug collection displayed on the wall. Schneider, PhD, professor of microbiology and immunology at the School of Medicine, has been collecting bugs since his childhood in Ottawa, Ontario.

"I've always loved biology," he said. When he was in 12th grade, he won first place in an international science contest, besting the future founder of Amazon, Jeff Bezos.

And you can't help but notice, atop a packed bookcase, an assortment of odd little wooden contraptions. They're kinetic sculptures that Schneider built to represent data that would otherwise be hard to comprehend.

"David's office is a unique environment that really reflects how unique he is," said Denise Monack, PhD, professor of microbiology and immunology, whose lab is adjacent to his. "He's extraordinarily creative."

If Schneider's office seems a bit busy, so is he. As chair of the Department of Microbiology and Immunology, he oversees a complex of 150 people. He also teaches and does a lot of research.

And his research generates lots of data, which is where the contraptions come in: Sometimes it makes more sense for him to plot that data in more than two dimensions. He calls his creations data sculptures.

Circular reasoning

Schneider focuses on infectious diseases and their effects on infected hosts. Getting sick and recovering are two different sides of a circular journey, he said.

"The path you take back to health isn't the path you take getting sick," he said. "It's a loop." The precise scientific term for this kind of loop is "hysteresis."

Not that the loop necessarily has to be represented as a circle. It could be depicted, for example, as a baseball diamond. When you first get infected, you're standing at home plate — analogous to your initial state of good health. Then the pitch comes — that is, you get infected by who knows what — and you, the infected host, respond in one of various ways, depending on the pathogen and on your initial condition: You swing and hit the ball to left field, you bunt or the umpire calls, "Ball four!" In any case, you're on your way to first base. At this stage, the pathogen load is increasing, and your immune system is kicking in and making you feel worse. By the time you reach second, you're at your maximum point of sickness.

Recovery is analogous to scoring a run, having rounded all those bases. However, you can't score, or return to full-blown health, by going in reverse from second base back to first and then home. Very different things are happening in your body when you're approaching or standing on third base as opposed to first base. And though, from the stands, those two bases may appear juxtaposed, it would be a mistake to think first base and third base are equivalent. The internal states of the players standing on those bases are quite different. You might want to give the third-base patient an entirely different set of medications from those suitable for a first-base patient. Maybe you should give one antimicrobials and rehydrate the other.

Take malaria. When infected humans or mice are at their sickest, they're already well on their way to eliminating the microbes that cause the disease.

"Malaria infects somewhere over 200 million people

See SCHNEIDER, page 7

IPS cells probed as potential cancer vaccine

By Krista Conger

Induced pluripotent stem cells, or iPS cells, are a keystone of regenerative medicine. Outside the body, they can be coaxed to become many different types of cells and tissues that can help repair damage due to trauma or disease. Now, a study in mice from the School of Medicine suggests another use for iPS cells: training the immune system to attack or even prevent tumors.

The results suggest it may one day be possible to vaccinate an individual with his or her own iPS cells to protect against the development of many types of cancer.

STEVE FISCH

Joseph Wu and his team found that injecting mice with induced pluripotent stem cells helped train the animals' immune systems to attack tumors.

The iPS cells work as an anticancer vaccine because, like many cancer cells, they resemble developmentally immature progenitor cells, which are free from the growth restrictions built into mature cells that make up the body's tissues. Injecting iPS cells that genetically match the recipient, but that are unable to replicate, can safely expose the immune system to a variety of cancer-specific targets, the researchers found.

"We've learned that iPS cells are very similar on their surface to tumor cells," said Joseph Wu, MD, PhD, director of Stanford's Cardiovascular Institute and professor of cardiovascular medicine and of radiology. "When we immunized an animal with genetically matching iPS cells, the immune system could be primed to reject the development of tumors in the future. Pending replication in humans, our findings indicate these cells may one day serve as a true patient-specific cancer vaccine."

Wu is the senior author of the study, which was published online Feb. 15 in *Cell Stem Cell*. Former postdoctoral scholar Nigel Kooreman, MD, is the lead author.

"These cells, as a component of our proposed vaccine, have strong immunogenic properties that provoke a system-wide, cancer-specific immune response," said Kooreman, who is now a surgery resident in the

See IPS, page 6

Low-fat or low-carb? It's a draw, study says

By Hanae Armitage

New evidence from a study at the School of Medicine might dismay those who have chosen sides in the low-fat versus low-carb diet debate.

Neither option is superior: Cutting either carbs or fats shaves off excess weight in about the same proportion, according to the study. What's more, the study inquired whether insulin levels or a specific genotype pattern could predict an individual's success on either diet. The answer, in both cases,

See DIET, page 7

SYDA PRODUCTIONS / SHUTTERSTOCK.COM

Specific set of nerve cells controls seizures' spread through brain

By Bruce Goldman

Experimental activation of a small set of nerve cells in the brain prevents convulsive seizures in a mouse model of temporal lobe epilepsy, the most common form of epilepsy among human adults, according to a study by researchers at the School of Medicine.

In contrast, inactivating these cells, known to neuroscientists as mossy cells, facilitates the spread throughout the brain of the electrical hyperactivity initially localized at a seizure's onset, causing the full-blown behavioral symptoms of temporal lobe epilepsy.

Ivan Soltesz

Inactivating this nerve-cell population also induces the same cognitive losses that characterize chronic, drug-resistant temporal lobe epilepsy in humans, the scientists found.

Epilepsy affects 65 million people worldwide, with 150,000 new cases diagnosed annually in the United States alone. Three out of five of those affected suffer from temporal lobe epilepsy. Progressive loss of mossy cells is a hallmark of this disorder.

Mossy cells are known to be damaged easily as a result of head trauma and decreased blood supply. Such brain injuries, in turn, increase the risk for temporal lobe epilepsy.

The role of mossy cells in epilepsy has perplexed neuroscientists for a couple of decades. The new Stanford study, which was published Feb. 16 in *Science*, offers an explanation. And it points to an entirely new entry point for developing drugs that could bring therapeutic relief to people with chronic, drug-resistant epilepsy, a debilitating condition that not only circumscribes patients' lifestyles and occupational options but predisposes them to depression, anxiety and early death.

"It should, in principle, be possible to develop targeted therapies directed at mossy cells to control both seizures and the resulting cognitive deficits," said Ivan Soltesz, PhD, professor and vice chair of neurosurgery and the senior author of the study. "This would be great, because the 20 or more compounds now approved for treating patients fail 30 to 40 percent of the time."

The study's lead author is Soltesz's former graduate student Anh Bui, PhD, now a medical student at the University of California-Irvine.

An electrical storm in the brain

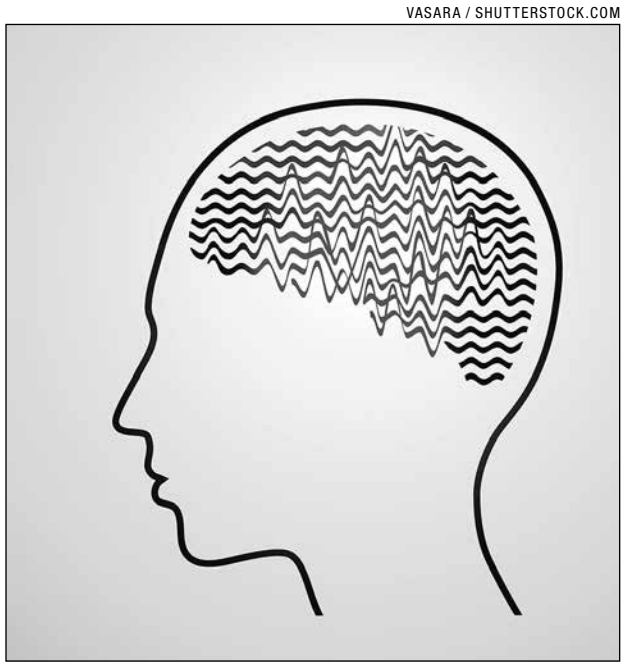
Epileptic seizures are sometimes described as an electrical storm in the brain. These storms typically begin at a single spot in the brain, called the focus, where nerve cells — for reasons that remain unclear — begin repeatedly firing in synchrony. All too often they spread from the focus to widespread areas throughout the brain, a process called generalization. It's this brain-wide hyperactivity that causes the classic behavioral symptoms of epileptic seizures, such as loss of consciousness, convulsions and disordered thinking.

The exact location of the epileptic focus in the brain varies from individual to individual. In the great majority of patients with temporal lobe epilepsy, the focus lies in the hippocampus, a much-studied, seahorse-shaped midbrain structure that's crucial to spatial navigation and to encoding new experiences into long-term memory.

Mossy cells, found exclusively in one section of the hippocampus, are few in number, but each connects with tens of thousands of other hippocampal nerve cells. Via these connections, mossy cells can stimulate a multitude of excitatory hippocampal nerve cells, whose output extends to other sections of the hippocampus. But they can also stimulate an opposing class of cells that inhibit these excitatory cells. Whether the net effect of mossy-cell activity is to promote or counter overall output of the excitatory nerve cells has, until now, been an open question.

To answer the question, Soltesz, who holds the James R. Doty Professorship of Neurosurgery and Neurosciences, and his colleagues turned to a mouse model of temporal lobe epilepsy.

VASARA / SHUTTERSTOCK.COM



Temporal lobe epilepsy is the most common form of epilepsy among adults. New findings from Stanford indicate that therapies aimed at specific cell types in the brain may be able to treat the condition.

The mice the Stanford investigators used were bioengineered so that their mossy cells responded to pulses of light, conveyed to those cells via an implanted optical fiber. Blue light caused mossy cells to fire, while amber light caused them to resist firing. So, by flipping a laser switch, the scientists could activate or inhibit the mice's mossy cells at will. (This increasingly widespread experimental technique, called optogenetics, is noteworthy for its capacity to target specific sets of nerve cells in order to reveal their function.) The scientists also recorded activity in the hippocampal region where mossy cells reside.

Effects of inhibiting, exciting mossy cells

Soltesz, Bui and their colleagues showed that inhibiting mossy cells, while not increasing the frequency of spontaneous episodes of hyperactivity in the focus of the chronically epileptic mice, did lead to a substantial increase in the number of seizures that spread from the focus to larger areas of the brain. Conversely, excitation of mossy cells in these mice diminished the number of generalized, outwardly visible seizures while having no effect, or merely a minor one, on the frequency of purely focal seizures.

In a memory test that gauges a mouse's recognition of unfamiliar objects, the epileptic mice, despite having lost more than half of their mossy cells, did fine. But they failed another test that assesses their ability to notice when a familiar object has been moved — a gauge of spatial memory, which suffers a decline in chronic temporal-lobe epilepsy. When the Stanford scientists also subjected optogenetically engineered but otherwise normal mice to these tests, they did great — until the researchers inhibited their mossy cells, at which point these animals' spatial recall headed south, too.

"We've shown that mossy cells' role is protective in preventing the spread to other brain regions of seizures that originate in the hippocampus, the dominant focal site for seizures associated with temporal lobe epilepsy," said Soltesz. "Drugs targeting mossy cells in patients with chronic, drug-resistant cases may someday be able to reduce the incidence of convulsive seizures enough to give patients' back some of their lost lifestyles."

Such interventions might serve as an alternative to demanding surgical procedures now employed to excise the seizure focus from patients' brains, Soltesz said.

Other Stanford co-authors of the study are life science research professionals Theresa Nguyen and Sylwia Felong; postdoctoral scholars Charles Limouse, PhD, and Mattia Maroso, PhD; and basic life research scientists Hannah Kim, PhD, and Gergely Szabo, PhD.

The study was funded by the National Institute of Neurological Disorders and Stroke.

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

Mental rehearsal prepares our minds for real-world action, study finds

By Nathan Collins

When people visualize themselves doing well at an activity, like ice skating, their chances of success at that activity improve. It's called mental rehearsal, and psychologists and athletes alike know that it works.

Now, Stanford researchers report that they've discovered how the brain learns physical tasks, even in the absence of real-world movement, and found that this ability could hinge on getting the mind to the right starting place, ready to perfectly execute everything that follows.

"Mental rehearsal is tantalizing, but difficult to study," said Saurabh Vyas, a graduate student in bioengineering. That's because there's no easy way to peer into a person's brain as he imagines himself racing to a win or practicing a performance. "This is where we thought brain-machine interfaces could be that lens, because they give you the ability to see what the brain is doing even when they're not actually moving," he said.

A paper describing the research was published Feb. 15 in *Neuron*. Vyas is the lead author. The senior author is Krishna Shenoy, PhD, professor of electrical engineering and the Hong Seh and Vivian W. M. Lim Professor.

Although there are some important caveats, the results could point the way toward a deeper understanding of what mental rehearsal is and, the researchers believe, to a future in which brain-machine interfaces, usually thought of as prosthetics for people with paralysis, are also tools for understanding the brain, Shenoy said.

What are you thinking?

The idea for the study came while thinking about how people learn to use brain-machine interfaces to perform a task, Vyas said. In a typical setup, a person — or, very often, a monkey — has to learn to move a cursor around a computer screen using only patterns of activity in his or her brain, not by using hands or other movements. That got Vyas wondering whether what people (or monkeys) learned using brain-machine interfaces might somehow transfer, in a way similar to mental rehearsal, to physical movements.

"He's just sitting there thinking, and as he's thinking he's getting better and better" at moving the cursor, Vyas said, referring to one of the monkeys he studied. "The natural question becomes: What happens if you switch to another context, where now he actually has to generate muscle activity? Do you see the effects of that learning in that new context?"

The short answer is yes: Mental learning does transfer to physical performance. Vyas initially taught two monkeys outfitted with brain-machine interfaces to move a cursor from one place to another on a computer screen using only their minds, then introduced a complication, called a visuomotor rotation: What mental signals they previously used to move a cursor up would now move it at an angle of, say, 45 degrees clockwise. The monkeys easily adapted, and that adaptation carried over when they repeated the same task using their hands, rather than the brain-machine interface, to control the cursor directly. Now, if the monkeys wanted to move the cursor up, they moved their hands 45 degrees clockwise.

This suggested that the monkeys were doing something like mental rehearsal, Vyas said; what they had learned to do in their minds, they could then do with their hands. Some additional experiments and an analysis of recorded neural activity suggest the reason why: Rehearsing the task

See REHEARSAL, page 8

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
3172 Porter Drive
Palo Alto, CA 94304
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

Paul Costello
Chief communications officer
Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu. Please also contact him to receive an e-mail version of *Inside Stanford Medicine*.

STANFORD MEDICINE

5 QUESTIONS

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

John Ioannidis on antidepressant efficacy

Some 350 million people globally are currently diagnosed with depression, making it the world's leading psychiatric disorder. As many physicians and patients opt to use drug-based therapy, pharmaceutical companies have churned out a variety of antidepressants.

An international team of researchers specializing in fields such as psychiatry, public health and statistics conducted an in-depth analysis of more than 500 clinical trials that tested any of 21 different antidepressants. The group found that all 21 drugs were modestly more effective than a placebo — a validation for the overall efficacy of pharmacological treatment of depression.

The results of the meta-analysis, which were published online Feb. 21 in The Lancet, *bring new evidence and insights to drug-based depression therapies, and could provide a valuable resource for doctors and patients sorting out antidepressant options.*

John Ioannidis, MD, DSc, professor of medicine and co-director of the Meta-Research Innovation Center at Stanford, is an author of the study, which he said offers the best currently available, evidence-based guide for antidepressant treatments.

Recently, writer Hanae Armitage asked Ioannidis, an expert on improving the reliability and reproducibility of scientific research, to discuss the results of the analysis and what it means for navigating the pharmacological treatment of depression.

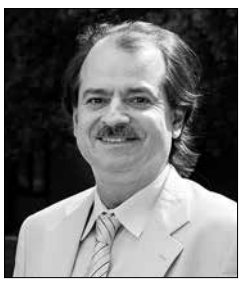
1 What new light does this study shine on antidepressant treatment and antidepressants generally?

IOANNIDIS: Antidepressants have been one of the most widely used, misused and debated classes of drugs. Major depression is a huge problem, and having the best information available to make decisions on how to treat patients is totally essential. Relevant evidence has typically been highly fragmented and biased, which has not helped resolve the misuse of these medications or settle the debates about them. By putting together cleaned, standardized data from more than 116,000 patients and 522 randomized trials, and by using the highest possible standards of analysis, we can offer some concrete evidence to inform the proper use of 21 different antidepressants.

2 What would you say are the biggest takeaways of this analysis from the perspective of a clinician? What about from the perspective of a patient with depression?

IOANNIDIS: Some key lessons are, first, that for acute depression in adults, antidepressants are effective, modestly so. Second, when a new drug is tested against an older one, there is sometimes bias favoring the newer drug — and the newest drugs should not necessarily be the top choice. Third, bias does not completely account for the efficacy of antidepressants. They do have a role in treating major depression. All 21 antidepressants that we assessed are better at treating depression than placebo, although the benefit is, on average, quite modest. Moreover, almost all of them are more acceptable, meaning that they are better tolerated, than placebo. (Acceptability is a measure that typically combines the impact of toxicity and the perceived efficacy.)

Finally, different agents have different profiles of efficacy and acceptability. Our study shows the relative merits and harms of each of the 21 antidepressants compared against one another. Some of them seem to be better, or more acceptable, although the differences between them are less pronounced when we compare them against placebo.



John Ioannidis

A patient can discuss this information with his or her physician and make a choice to start a specific antidepressant, if it is indicated, with some particular evidence-based expectations in mind. Of course, different patients may still respond differently, and this is difficult to predict ahead of time. But at least there is sensible and congruent information that informs patients on the average response that he or she can expect to have if taking one of these antidepressants.

3 How can doctors use this information to better navigate treatment for their patients?

IOANNIDIS: Doctors may find it difficult or confusing to sift through the results of more than 500 trials in the literature, many of which may only be published in a fragmentary fashion or not at all. The network analysis offers a condensed version of the evidence, and they can quickly see where a specific drug is mapping itself in terms of efficacy, acceptability and other outcomes of interest. Hopefully, this will make decision-making easier and more appropriate.

4 What other classes of drugs do you think could benefit from this type of analysis?

IOANNIDIS: For most types of drug treatments and most diseases, evidence is fragmented across a large number of mostly small and inconclusive trials, and there is substantial evidence that many of these trials are either left unpublished or have selective reporting of their outcomes. Large network meta-analyses that examine the entire body of evidence of all available drug treatments for various diseases, that make a systematic effort to unearth all the data and clean the results, would be very useful to perform across all medical specialties. There is an increasing number of papers that do perform network meta-analyses, but most of them look at snapshots of the evidence, consider some but not all the possible available treatments and make little or no effort to get unpublished results unearthed.

5 Do you think the results of this study carry implications for drug developers moving forward?

IOANNIDIS: Even though depression is very common, and thus the market for effective and well-tolerated drugs is very large, there has been a slowing of research and development of new drugs in this field. Our analysis clearly shows that there is a lot of room for improvement — both in efficacy and in acceptability compared with the currently available treatments. Thus, focusing on developing new drugs would be welcome, and our analysis can provide a yardstick of what the currently available drugs can achieve for comparison. It also shows that differences between available drugs are modest, therefore new research is needed to find drugs that use very different modes of action and may thus achieve better results. **ISM**

At second finance town hall, a more detailed look at medical school revenue sources and expenses

Of the $115 million the School of Medicine spent on operating and maintaining the buildings it occupied in fiscal year 2017, $41 million went toward rent, and $25 million went toward utilities — things like electricity and water. The medical school also finished that year with a consolidated budget surplus of $116 million.

These are just a few of the many facts Samuel Zelch, MBA, chief financial officer and associate dean for fiscal affairs at the school, shared Feb. 14 during a lunchtime presentation. The event, held at the Li Ka Shing Center for Learning and Knowledge, was the second of a three-part series of town hall meetings aimed at giving school employees the opportunity to learn and ask questions about the school's finances.

In introductory remarks at the first meeting, which was held in the fall, Dean Lloyd Minor, MD, said, "We'll all be able to do a better job of stewarding and managing our resources responsibly if we understand where those resources are coming from and where they sit and what they're intended for."

At the first meeting, Zelch gave a broad overview of the school's finances; this time, he briefly recapped that overview before focusing on the revenues and expenses of units funded through the Dean's Office; university cost recovery; the costs of facilities maintenance, capital projects and debt service; and the revenue-sharing formula used to fund departments, programs and support for faculty. Among other takeaways:

JOHN SANFORD

Samuel Zelch, Marcia Cohen and Lloyd Minor answered questions at the Feb. 14 town hall meeting.

- The school covers all of its own expenses and also pays a percentage on most of its revenue — 5.68 percent on about $2.1 billion in fiscal year 2017 — for services provided by the university. This fee is called the university cost recovery.
- Over the next decade, most of the school's capital expenditures will go toward three major building projects: the first of two Biomedical Innovation Buildings, the first of two Centers for Academic Medicine, and the Cancer Research and Precision Health Building.
- Total funding from the Dean's Office to departments, programs and faculty support was more than $103 million in fiscal year 2017.
- The capital project plan through 2036 totals $2.3 billion.

Minor, Zelch and Marcia Cohen, MBA, senior associate dean for finance and administration, also fielded questions from the audience following the presentation.

For more information about the topics discussed at the meeting, the slide presentation shown at the town hal can be viewed at http://med.stanford.edu/fiscalaffairs/controller.html (SUnet ID required). On its website, the school's Office of Fiscal Affairs has posted a link where employees can pose questions or suggest topics they would like to see covered at the third finance town hall meeting, which is scheduled for April 3. **ISM**

Stanford Drug Discovery Conference set for April 23-24

Registration is open for the 2018 Stanford Drug Discovery Conference, which will take place April 23-24 at the medical school's Li Ka Shing Center for Learning and Knowledge.

The conference will bring together experts in drug discovery to discuss a broad range of policy, research and business opportunities. Speakers will include leaders in drug discovery from academia, industry and government.

A lifetime achievement award will be presented to Roy Vagelos, MD, chair of Regeneron Pharmaceuticals Inc.

Multiple representatives from biotechnology and pharmaceutical companies will be speaking during a session titled "View From the Top," including Ken Frazier, CEO of Merck; Bob Bradway, CEO of Amgen; and Joseph Jimenez, former CEO of Novartis.

"The Drug Discovery Symposium will be a unique opportunity for Stanford trainees and faculty to network with pioneers in translational research, gain insight into new opportunities from federal and foundation policymakers, and learn from the experiences of corporate leaders in the pharmaceutical industry," said Joseph Wu, MD, PhD, professor of medicine and director of the Stanford Cardiovascular Institute.

Applications are being accepted for translation-stage projects to be presented "Shark Tank"-style to a panel of scientists, CEOs and entrepreneurs.

Admission to the conference for academics is $50. For others, it's $250. For more information or to register, visit http://med.stanford.edu/cvi/mission/upcoming-events/2018-drug-discovery-conference.html. **ISM**

Iron triggers dangerous infection in lung transplant recipients

By Nicoletta Lanese

Researchers at the School of Medicine have identified elevated tissue iron as a risk factor for life-threatening fungal infections in lung transplant recipients.

The study, reported Feb. 21 in *Science Translational Medicine,* investigated why lung transplant patients are more vulnerable to this fungus, *Aspergillus fumigatus*. "People rarely think about how a change in the patient's body tissues might make it better ground for invasion," said Mark Nicolls, MD, professor of pulmonary and critical care medicine and senior author of the study. Informed by this research, Nicolls has proposed a potential new approach for curbing these infections.

Aspergillus fumigatus is an extremely common mold, prevalent in even the most pristine hospital settings. "It's everywhere — we inhale thousands of these spores per day," said Joe Hsu, MD, assistant professor of medicine and lead author of the study. One-third of lung transplant recipients develop *Aspergillus*-related diseases, including severe asthma and often-fatal lower respiratory infections. The leading cause of death among these patients is transplant rejection, which the mold accelerates dramatically.

LIBERO AJELLO / CENTERS FOR DISEASE CONTROL AND PREVENTION

Aspergillus fumigatus **is a common mold, prevalent in even pristine hospital settings.**

There are many risk factors for *Aspergillus* infection that are difficult to address in lung transplant recipients. Transplant patients are given medications that leave them less able to ward off infections, but without these drugs, their immune systems would attack their new lungs. During recovery, patients have no ability to cough up invading pathogens, making them especially vulnerable to the omnipresent spores. This is because the lung transplant procedure disrupts signals from the vagus nerve, which controls the cough reflex. Patients are usually put on antifungal medications in an attempt to prevent infection, but these pathogens are becoming more drug-resistant over time.

'Like fertilizer for Aspergillus'

All lung transplants carry these known risks, but not all lung transplants result in *Aspergillus* infections. Something causes the organism to behave differently in cases of infection, Hsu said. The study identified iron as a critical factor. "Iron is like fertilizer for the *Aspergillus*," Nicolls said.

Hsu was interested in finding the *Aspergillus* trigger switch — the factor that prompts it to invade tissue. He studied the pathogen in mouse models by transplanting windpipes from one mouse to another. Observing the rejection process, he found that the transplanted tissue bled and accrued high levels of iron. Hsu biopsied human transplant patients and found the same distribution of iron, with higher levels in the transplanted tissue than the host. Thinking he may have found the trigger, Hsu introduced *Aspergillus* into the mice, comparing how it acted with and without access to iron.

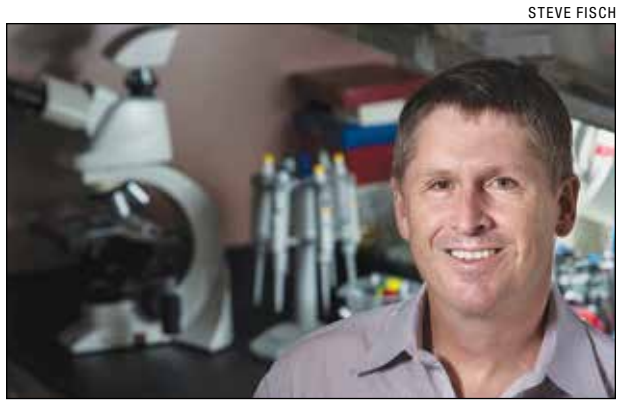
He found that elevated iron prompted *Aspergillus* to invade. In experimental conditions that provided the pathogen more iron, it invaded the transplant. The more iron, the deeper the invasion progressed into the tissue. The results indicate increased iron is a major determinant of *Aspergillus* invasion. Differences in iron levels between transplant patients seem to explain why some become infected while others don't. "You could have lots of *Aspergillus* in the airway, which is fine because its everywhere, but it wouldn't penetrate the tissue unless there was iron beneath it," Nicolls said.

A potential treatment

The study suggests infection can be prevented by starving the *Aspergillus* organism of iron. Without iron to fuel it, the mold doesn't invade. The depth of invasion decreased in mice injected with an iron-reducing chemical. The result suggests a novel treatment route. Rather than targeting *Aspergillus* itself, doctors could modify tissue iron levels to change the organism's behavior, Hsu said. His next step is to study this treatment approach in humans, he said. High iron is characteristic of other pulmonary diseases, and Hsu predicts this methodology may be applicable across the field of pulmonary care.

Nicolls is an inventor on a new patent describing how lung transplant blood vessels may benefit from a low-iron environment, a property that could also include preventing mold invasion. He developed the technology with a number of collaborators, including Geoffrey Gurtner, MD, professor of surgery at Stanford, and Jayakumar Rajadas, PhD, director of Stanford's Biomaterials and Advanced Drug Delivery Lab, who is also a co-author of the study. The patent is a chemical solution that captures excess iron so the pathogen cannot use it. Nanoparticles act as a vehicle to transport the chemicals into the body.

STEVE FISCH



Mark Nicolls is the senior author of a study showing that elevated iron levels in the tissue can make lung transplant patients vulnerable to infection from a fungus called *Aspergillus fumigatus*.

"The capacity to deliver these compounds directly to the lungs is novel," Hsu said. "For the first time, we have a new way to treat these infections aside from antibiotics that try to wipe out the organism itself." The solution can be applied like a paint during surgery, inhaled into the lungs or injected intravenously.

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-affiliated co-authors of the study are Karl Clemons, PhD, senior lecturer in medicine; Mohammed Inayathullah, PhD, basic life research scientist; Raymond Sobel, MD, professor of pathology; Hasan Nazik, MD, visiting research scholar; Venkata Pothineni, PhD, basic life science research associate; Shravani Pasupneti, MD, postdoctoral scholar; and David Stevens, MD, professor of medicine.

Researchers at the Veterans Affairs Palo Alto Health Care System, Medical University Innsbruck and University of Maryland School of Medicine also contributed to the study.

The work was supported by the National Heart, Lung and Blood Institute; the Austrian Science Foundation; and the Parker B. Francis Family Foundation.

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

Five-year neuroscience awards named in honor of Ben Barres

By Ruthann Richter

The Chan Zuckerberg Initiative, a Palo Alto-based philanthropic organization, has launched a major research effort to inject fresh energy, ideas and talent into understanding the basic biology of neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, the organization announced Feb. 20.

The research will be funded through two programs, including one that will support early career investigators willing to pursue bold, innovative ideas. These five-year awards, known as the CZI Ben Barres Early Career Acceleration Awards, are named in honor of Ben Barres, PhD, a distinguished Stanford neuroscientist who died in December at the age of 63.

CZI will also fund a series of collaborative science awards — three-year grants for small, interdisciplinary groups of scientists, clinicians and engineers working together on innovative high-risk, high-impact projects in basic science.

'A spiritual guide'

Both grant programs are part of CZI's new Neurodegeneration Challenge Network, which aims to fill in the gaps in the still-limited understanding of the basic cellular and molecular mechanisms behind these devastating illnesses.

Cori Bargmann, PhD, president of Chan Zuckerberg Science, said the group chose to name the young investigator awards in Barres' honor because he was "a spiritual guide" for the work. An advocate for basic science and for the mentorship of young researchers, Barres had been an adviser to CZI since its inception in 2015 and had a hand in helping craft the awards program, Bargmann said.

"Ben was a truly exceptional scientist and human being. He exemplified the values of the Chan Zuckerberg Initiative, especially our work in neurodegenerative disease. His commitment to collaboration between basic science and medicine, his creative work in neurodegeneration, and his advocacy for women, underrepresented groups and young scientists inspire us all," Bargmann said.

Barres made significant discoveries about the role of glial cells, the underrecognized cells that comprise the majority of brain cells, and in doing so revolutionized the field of neuroscience. A professor of neurobiology, of developmental biology and of neurology, he was widely praised for the passion he brought to his work.

Barres was particularly known for his dedication to his trainees and was a champion for basic science, helping establish the Master of Science in Medicine program at Stanford to teach PhD students about human biology and disease and thus prepare them to turn new discoveries into clinically useful treatments.

Ben Barres

"Ben was a selfless and steadfast champion of young researchers. As his colleague and friend, I am moved that these awards will commemorate him and continue his legacy of celebrating and supporting early-career scientists," said neuroscientist Marc Tessier-Lavigne, PhD, president of Stanford University.

'A remarkable person'

Lloyd Minor, MD, dean of the School of Medicine, said the awards "are an inspired way to honor the memory of Ben, a remarkable person and a beloved mentor who embodied the spirit of the awards in his brilliance, creativity and passion for neuroscience."

The CZI Ben Barres Early Career Acceleration Awards are open to scientists throughout the world working in a variety of disciplines. The awards are open to MDs and PhDs who are new to the field of neurodegeneration. Awardees will receive $500,000 a year for five years, for a total of $2.5 million. The collaborative science awards will provide recipients with $350,000 a year for three years, or a total of $1.05 million.

CZI was founded by Silicon Valley couple Priscilla Chan, MD, and Mark Zuckerberg, chairman and CEO of Facebook, to advance science, education and social justice. One of CZI's first initiatives was the creation of the Chan Zuckerberg Biohub, an independent nonprofit research center supported by $600 million over a 10-year period. The center brings together physicians, scientists and engineers at Stanford, UC-San Francisco and UC-Berkeley to engage in innovative scientific exploration and invent new tools to advance discoveries.

Information about the awards is available at https://chanzuckerberg.com/science/rfa. ISM

Patients and caregivers share their experiences through Storybank

By Mandy Erickson

"I clearly remember the day you told me there was a lump in your breast," Margaret McCulloch, 52, told her best friend, Jackie Fitzpatrick, 54.

The two were sitting in an improvised recording studio on the third floor of Stanford Cancer Center South Bay. Esther Chyan, RN, a supportive care manager, was working the audio, ensuring their conversation recorded clearly. Bryanna Gallaway, director of service excellence, provided information and forms in preparation for the recording session, and was ready to facilitate the conversation should it need any additional guidance.

But there was no need for facilitating; once the two got going, they recounted Fitzpatrick's cancer treatment journey as if they were sitting on a porch, reminiscing over a bottle of rosé.

McCulloch recounted how she reassured her friend not to worry, but "when I got the phone call that you were diagnosed with stage-4 breast cancer, my heart sank," she said.

Fitzpatrick had invited McCulloch to join her in volunteering for a storytelling marathon that took place last October at the San Jose Stanford Cancer Center facility. They participated in the Stanford Storybank program, which Stanford Health Care is conducting in partnership with StoryCorps, a national organization whose mission is to capture, honor and preserve stories about human experiences through audio interviews. The recording equipment can be taken to any SHC location.

PAUL SAKUMA

Margaret McCulloch (left) and Jackie Fitzpatrick recounted how Fitzpatrick's breast cancer diagnosis discussed their friendship. They recorded their conversation as part of the Stanford Storybank project.

Each conversation features two people — a patient and a family member, for example, or two SHC employees — and lasts 40 minutes. If the two people agree, the conversation will be archived within the U.S. Library of Congress, and edited down to shorter story segment clips for use by SHC.

The Stanford Storybank was launched to create a space for patients, families and staff to share their experiences, providing an opportunity for all to learn, connect, heal and inspire. It's built on the premise that everyone has a story to share, and provides a platform to amplify the voices of the SHC community.

As of Feb. 1, 35 stories have been recorded. The Service Excellence team posts the edited audio clips on the SHC intranet, shares them during management meetings and presents them during orientation or staff training sessions. The conversations "bring us back to why we're here, why we do what we do," said Alpa Vyas, vice president of patient experience.

The team also posts a "story of the month" that's available on SoundCloud at https://soundcloud.com/search?q=stanford%20storybank.

Cathartic conversations

While instructing Fitzpatrick and McCulloch before the recording began, Gallaway told them, "It's OK to cry; it's OK to laugh; it's OK to do anything you would normally do in a conversation."

The two friends, who met 12 years ago when their children were in the same kindergarten class, discussed the effect Fitzpatrick's cancer, diagnosed six years ago, has had on their lives and their friendship.

"How do you distract your mind, not to think about cancer 24/7?" McCulloch said.

"I don't dwell on the negative stuff," Fitzpatrick said.

"I admire that about you," McCulloch said.

"The one thing that cancer has given me is a clear, concise view on my family and what's important to me," Fitzpatrick continued. "I made amends with people I needed to make amends with. It's a blessing. It's been a difficult journey, but it's kind of worth it."

The two laughed about how Fitzpatrick's hair grew back white after a round of chemotherapy and she looked like Annie Lennox. "I kind of had fun with it," she said.

Turning serious, she asked McCulloch, "What's it like for you? I sometimes think it's harder for the people not going through it."

"Sometimes I think that I'm weak. I want to make you better, but I can't," McCulloch confessed.

After the recording session was over, the two friends described the conversation as cathartic.

Fitzpatrick said she hoped participating in the Stanford Storybank program would help other people diagnosed with cancer. "I really want to provide hope to people in the same situation," she said.

The Stanford Storybank stories will be archived on SHC Connect and stored in the Library of Congress. For information on how to participate in the Stanford Storybank, contact cicare@stanfordhealthcare.org. **ISM**

Magazine explores challenges of breaking boundaries in science

By Patricia Hannon

If the tale of Dr. Victor Frankenstein and his hideous creation reminds us of anything, perhaps it's that being human means more than simply having a beating heart and a working brain. The relationship between the obsessed doctor and the unnamed monster depicted in Mary Shelley's book also reminds us that being human also should mean being humane.

In his introduction to the new issue of *Stanford Medicine* magazine, Lloyd Minor, MD, dean of the School of Medicine, discusses how the novel's desperate and lonely creature, who wants only to be understood, can help illustrate why humanity must help inform science and discovery.

"It is through this nuanced, complex character that we feel compassion and a deep empathy," Minor said. "At Stanford Medicine, empathy is vitally important to our vision of precision health, which brings together the high tech and the high touch, and recognizes the uniqueness of every individual."

Frankenstein themes that still matter

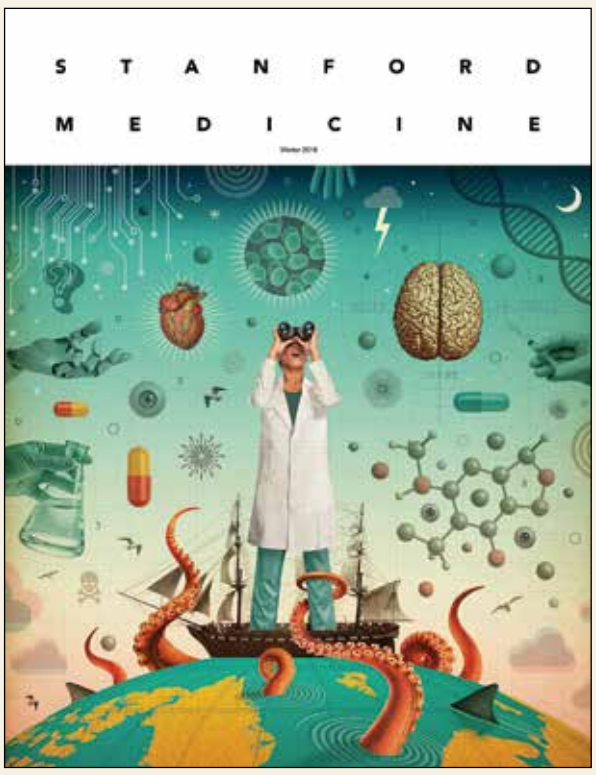
The magazine's issue delves into research that pushes boundaries in medicine, but it also looks at the implications of that research on humanity — *Frankenstein* themes that still matter 200 years after Shelley published her tale.

The ethical and cultural challenges of charting medicine's "out there" frontiers are evident in several stories in the issue:

• Audrey Shafer, MD, notes that "many scientists, doctors and patients balk at any mention of the words *Frankenstein* and medicine in the same breath." But they must not shy away from the moral and ethical questions raised by the novel, and by science itself, as we probe what it means to be human, said Shafer, professor of anesthesiology, perioperative and pain medicine, and director of the Stanford Medicine and the Muse program. The program is highlighting the novel's themes through a yearlong series of courses, film screenings and other events.

• Hiromitsu Nakauchi, MD, PhD, professor of genetics, dreams of quickly growing transplantable human organs in large animals, such as sheep or pigs, to save people whose organs are failing. But the research has reignited a national discussion about the potential implications of blending animal and human cells.

• Neuroscientist Sergiu Pasca, MD, assistant professor of psychiatry and behavioral sciences, and his lab team are growing tiny brains balls in petri dishes so they can discover what goes wrong in the brains of people with neurological diseases, including autism, epilepsy and Parkinson's disease. Because further research could include transplanting the cells into mice, Pasca is "actively engaged" in conversations with other scientists about how to proceed in the quickly advancing field.



• Researchers believe that the ability of the gene-editing tool CRISPR to quickly remove, delete and repair defective genes could improve the lives of millions of people with inherited disorders. But many fear the consequences if safeguards aren't established. Those include the possibility of using it to create designer babies, or that ongoing experiments to alter the DNA of disease-spreading insects or genetically enhance crops could have unintended negative impacts.

• Stanford's first U.S. adult heart transplant was considered shocking 50 years ago. Though surgeon Norman Shumway, MD, wasn't the first in the world to transplant a human heart, continuing research by him, his team and his successors led to worldwide advances in the procedure.

• Science author Mary Roach talks about why she isn't squeamish about writing about the crevices of our bodies where few authors venture. "You hear a lot about the brain and the heart. People have a sense that these are miraculous, but not so much the nether regions or the inside of the nose, the nostrils, the tongue. The icky parts are just as miraculous, and people tend to overlook them. I'm the plumber," she said.

Outside a space station

The issue also includes an excerpt from a book by physician-astronaut Scott Parazynski, MD, a medical school alumnus who wrote about the harrowing — and glorious — day he spent suspended outside the International Space Station Discovery to repair a ripped wing on the station's solar panels; and a story about the ideas that engineers, biologists and doctors are exploring to prevent the long-term disabilities suffered by people who've had strokes.

The magazine is available online at stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at (650) 723-6911 or by sending an email to medmag@stanford.edu. **ISM**

OBITUARY

Gerald Reaven, scientist who coined 'Syndrome X,' dies at 89

By Tracie White

Gerald "Jerry" Reaven, MD, who gained international recognition for coining the term Syndrome X — now known as metabolic syndrome — died Feb. 12 at his home on the Stanford campus. He was 89.

An endocrinologist and professor emeritus of medicine at the School of Medicine, Reaven was one of the first researchers to argue for the existence of insulin resistance, a diminished response to the hormone insulin. It was a controversial concept that met with huge opposition. But Reaven proved the naysayers wrong. In 1988, he also introduced the novel idea of a link between insulin resistance and a cluster of other metabolic abnormalities that together greatly increased the risk for cardiovascular disease, which he called Syndrome X.

Gerald Reaven

"Jerry Reaven was a true Stanford pioneer," said Lloyd Minor, MD, dean of the School of Medicine. "He was the consummate scientist whose rigorous scholarship was a model for researchers at Stanford and around the world. He will be missed."

Never one to back down from a fight, Reaven broke ground when he argued for the existence of insulin resistance as an early and critical link in the development of Type 2 diabetes and conducted numerous studies over many decades proving the existence of insulin resistance and its many implications for metabolic diseases and cardiovascular diseases.

"Jerry Reaven was a giant in the Department of Medicine," said Robert Harrington, MD, professor and chair of medicine at Stanford. "His scientific contribution in describing and then further defining insulin resistance is one of the great achievements in metabolic disease over the last 50 years."

Insulin resistance controversy

In the 1950s, when Reaven started out as a researcher, it was believed that there was only one type of diabetes and that it was caused by a lack of insulin.

"In the late '70s early '80s, there was a lot of controversy about insulin resistance, and Jerry was not shy about standing up and sharing his opinions," said Frederic Kraemer, MD, professor and chief of endocrinology, gerontology and metabolism at Stanford. "He was tenacious when it came to defending his scientific observations. He didn't like to accept opinions; he liked to accept facts — facts generated from well-controlled scientific investigations."

In 1988, during the American Diabetes Association Banting award lecture, he introduced the concept of the link between insulin resistance and other metabolic abnormalities, calling it Syndrome X. This constellation of conditions — increased blood pressure, high blood sugar and abnormal HDL cholesterol and triglyceride levels — later became known as metabolic syndrome and has become a useful indicator of increased risk for heart disease, stroke and diabetes.

Reaven continued to actively conduct research until October, when bad health finally kept him at home. He co-authored more than 800 papers in scientific journals and currently has at least two more in the pipeline. He was also the author of several books, including a popular book on Syndrome X and its repercussions on cardiovascular health. He was a mentor to many scientists both at Stanford and around the world.

'Science was his life'

"I visited him at his house just before the Super Bowl in February, when I knew he was sick," said Joshua Knowles, MD, an assistant professor of cardiovascular medicine. "He was very sad he couldn't be at work. I brought a paper on the effects of insulin resistance on different race and ethnicities. He wanted to see the data. Science was his life."

Reaven was a Midwesterner and a baseball fan. He was born in Gary, Indiana, on July 28, 1928, but grew up in Cleveland, which accounts for his lifelong "affection and frustration" with the Cleveland Indians baseball team, said his son, Peter Reaven, MD, an endocrinologist and director of the diabetes research program at the Phoenix Veterans Affairs Health Care System in Arizona.

"Both my dad and my mom were academics," he said. His mother, Eve Reaven, PhD, is a retired electron microscopist who lives in the Stanford home where she and Jerry raised their three children. "Often dinner conversations were about academics and science. Somehow that became comfortable."

But Peter said his father also made time for outside interests. Gerald Reaven loved sports, Broadway plays, jazz singers and literature. He traveled to Cuba when he was young to search for Hemingway. He always made the time to play sports with his children and continued to play on softball teams for many years. He was known for throwing birthday parties for faculty and staff, many of whom knew his favorite dessert was chocolate pie.

"He was a huge Cleveland Indians fan," said Knowles, who often heard broadcasts of the games coming from Reaven's computer at work. Knowles, who studies the genetic basis of insulin resistance, spoke of the many lessons he learned from Reaven over the years as both his trainee and colleague. Among them: "The fortitude to stick with an idea if you really believe in it, against external pressure" and "the need to find a scientific passion that keeps you coming to the lab on the weekend."

"Jerry was often the only faculty member here on Saturday and Sunday," Knowles said. "On many weekend mornings I would arrive after playing basketball and shoot the breeze with Jerry in his office. That dedication is infectious."

Reaven earned his undergraduate and medical school degrees at the University of Chicago and completed his residency training at the University of Michigan. He joined the Stanford faculty in 1960. He worked at the School of Medicine first in the endocrinology division and then, after semi-retirement, in the cardiovascular division. "He was an amazing thinker," said Sun Kim, MD, an associate professor of medicine who studies insulin resistance and diabetes. "He was a deep thinker who wanted the truth to be told. He loved work. He literally worked till the end."

Reaven won numerous awards, including the William S. Middleton Award for outstanding achievement in medical research from the Veterans Affairs Administration, the Banting Medal for Scientific Achievement from the American Diabetes Association, the Banting Memorial Lecture from the British Diabetes Association, the Fred Conrad Koch Award from the Endocrine Society, the Distinction in Clinical Endocrinology Award from the American Association of Clinical Endocrinologists, and the National Lipid Association Honorary Lifetime Member Award.

In addition to his wife and son, he is survived by daughters Marci Reaven of New York and Nancy Reaven of Los Angeles and their families.

In lieu of flowers, the family asks for consideration of a memorial donation to support the Gerald M. Reaven Memorial Research Fund at https://makeagift.stanford.edu or by making a check payable to "Stanford University" and sending it to Stanford University Development Services, P.O. Box 20466, Stanford, CA 94309-0466. Please note "In Memory of Dr. Gerald Reaven" online or on the memo line of the check.

A memorial service is being planned. ISM

IPS

continued from page 1

Netherlands. "We believe this approach has exciting clinical potential."

To make iPS cells, researchers collect cell samples from an easily accessible source like skin or blood. The cells are then treated with a panel of genes that make them rewind their developmental clock to become pluripotent, allowing them to become nearly any tissue in the body. One key test of pluripotency is the ability of the cells to form a tumor called a teratoma, which is composed of many different cell types, after the cells are injected into animals. (IPS cells used in regenerative-medicine therapies are grown in the presence of other proteins to encourage them to specialize, or differentiate, into specific cell populations before being used clinically.)

Cancer, iPS cells similar

Cancer cells also have long been known to echo many features of developmentally immature cells. As part of their cancerous transformation, they often shed the naturally occurring mechanisms that serve to block inappropriate cell division and instead begin proliferating rapidly.

Wu and Kooreman wondered exactly how closely iPS and cancer cells resemble one another. They compared the gene expression panels of the two types of cells in mice and humans and found some remarkable similarities, suggesting that these cells share proteins on their surfaces called epitopes that could serve as targets for the immune system.

To test this theory, they used four groups of mice. One was injected with a control solution, one received genetically matching iPS cells that had been irradiated to prevent the formation of teratomas, one received a generic immune-stimulating agent known as an adjuvant, and one received a combination of irradiated iPS cells and adjuvant. All animals in each group were injected once a week for four weeks. Lastly, a mouse breast cancer cell line was transplanted into the animals to observe the potential growth of tumors.

One week after transplantation, all mice were found to have developed tumors of the breast cancer cells at the injection site. Although the tumors grew robustly in the control groups, they shrank in size in 7 out of 10 mice vaccinated with iPS cells plus the adjuvant. Two of these mice were able to completely reject the breast cancer cells and live for more than one year after tumor transplantation. Similar results were obtained when Kooreman and his colleagues transplanted a mouse melanoma and mesothelioma (a type of lung cancer) cell line into mice.

Kooreman and his colleagues further found that immune cells called T cells from vaccinated mice were able to slow the growth of breast cancer cells in unvaccinated mice. Conversely, these T cells also blocked the growth of teratomas in mice injected with nonirradiated iPS cells, showing that the activated T cells were recognizing epitopes that are shared between the breast cancer cells and the iPS cells.

Putting immune system on alert

"This approach is particularly powerful because it allows us to expose the immune system to many different cancer-specific epitopes simultaneously," Kooreman said. "Once activated, the immune system is on alert to target cancers as they develop throughout the body."

> "Although much research remains to be done, the concept itself is pretty simple."

The researchers next would like to study whether the approach works in samples of human cancers and immune cells in a laboratory setting. If successful, they envision a future in which people could receive a vaccine comprised of their own irradiated iPS cells as a way to prevent the development of cancers months or years later. Alternatively, the iPS cells could potentially be used as a part of the standard of adjuvant care after primary surgery; chemotherapy or radiation therapy, or both; or immunotherapy as a way to treat established cancers.

"Although much research remains to be done, the concept itself is pretty simple," Wu said. "We would take your blood, make iPS cells and then inject the cells to prevent future cancers. I'm very excited about the future possibilities."

Other Stanford authors of the study are postdoctoral scholars Youngkyun Kim, PhD, Ning-Yi Shao, MD, PhD, Tzu-Tang Wei, PhD, Hyoju Yi, PhD, and David Paik, PhD; former postdoctoral scholars Patricia de Almeida, PhD, and Devaveena Dey, PhD; medical resident Vittavat Termglinchan, MD; former research assistant Raman Nelakanti; former research associate Arnold Han, MD, PhD; medical student Thomas Brouwer; instructor of medicine Idit Barfi, PhD; professor of microbiology and immunology Mark Davis, PhD; and professor of medicine Ronald Levy, MD.

The research was supported by the National Institutes of Health, the California Institute for Regenerative Medicine and a Korean R&D grant.

Stanford's departments of Medicine and of Radiology also supported the work. ISM

Schneider

continued from page 1

per year, making them really ill. About 400,000 of those people, mostly children, die every year," Schneider said. "We don't have a vaccine. There's resistance to almost all the drugs we have. We need new ways of fighting the disease."

Schneider's group has been doing experiments with malaria-infected mice, monitoring many aspects of their physiology over time. "And we notice, in these mice, that the levels of various cell types and immune-signaling chemicals in the blood go up and down as the animal gets sick, then recovers or dies. Potential drugs work only during a limited portion of this cycle."

What he's learned from his studies is that to treat a patient most efficiently, it would be great to know when the patient got infected. But that's somewhere between tough and impossible.

"We can't expect a child suffering from malaria to tell us when they were bitten by an infected mosquito," Schneider wrote in his study of malaria-infected mice and human patients published in *PLOS Biology* in 2016.

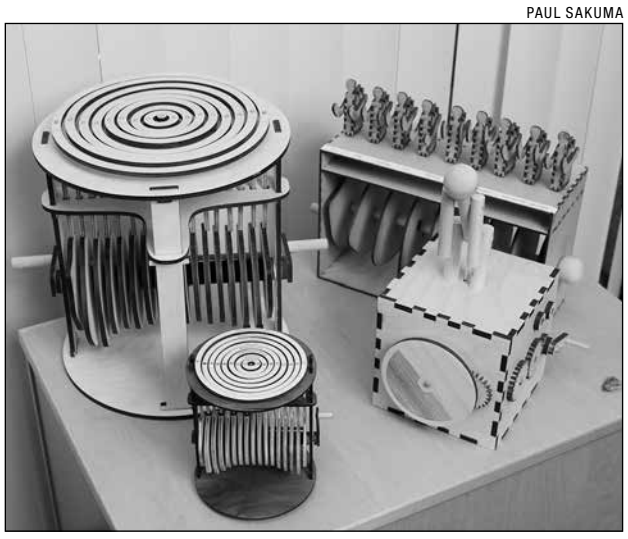
Ups and downs

That study showed that infecting mice with a malaria parasite resulted in a predictable set of changes, over time, in the blood levels of nine different cell types and immune-signaling substances as the mice first got sick and then recovered or, if they got too sick, were euthanized. By looking at the ratios and absolute levels of certain measured cell types and chemicals, the researchers could identify just where a mouse was along the looping path from health to sickness to recovery or death, and how likely it was to die barring further intervention.

In the same study, Schneider and his colleagues extended the findings to humans by looking at blood from children who had or hadn't been infected with malaria. Human infection, they showed, also follows a looping path, and the order of cellular and molecular ups and downs along that path rise and fall in the same sequence as in mice. That sequence provides a clue as to where a patient is in the sickness cycle, and factoring in the level of one or more blood markers in a patient might give you a good sense of how much danger he or she is in.

Nine is a big number. "If you're measuring nine things in a sick animal, it's hard to graph, not to mention grasp, nine different variables at one time," Schneider said. "You can lose some information. You want to emphasize that as one thing goes up, another comes down."

PAUL SAKUMA



An assortment of kinetic sculptures that Schneider has built to represent data that would be hard to comprehend in two dimensions.

Having encountered difficulty in communicating such multivariate, circular data findings, Schneider has turned increasingly to building data sculptures. One looks like a wooden rotisserie holding wooden pieces of "toast." The "rotisserie" is actually an open-front box. Its "skewer" is a long wooden axis running horizontally from one side of the box to the other side. The axis can be turned via an externally positioned crank.

The thin pieces of "toast" skewered inside the box are in fact slim disks, each irregularly shaped in its own particular way, that act as cams.

Each cam approximates a circle whose radius keeps changing at different points along the rim. The radius of a cam at any given point represents the level, at a particular point in the sickness/recovery cycle, of one of the nine cell types or substances Schneider's team measured in malaria-infected mouse blood.

Turning the crank

Astride each of the nine cams sits the figure of a man's torso. The men form a line along the box's top. When you turn the crank, they variously rise up, raising their arms to the heavens, or they sink down, arms back at their sides, as each is displaced idiosyncratically by its underlying, oddly shaped cam.

The left-most little man goes up, then the next, then the next, etc. Schneider turns the crank some more, and at some point the first little man starts to come back down even as the ones to the right of it are still rising. The rise and fall of the serially adjacent little men occur in a left-to-right ripple as the crank turns.

"It looks like a wave," Schneider said. "You might have missed that if you were looking at numbers or a graph, or just focusing on one point in time. But when you look at it this way, you can't help but see that there's a wave moving through the data over time."

By analyzing the ratios and phases and rates of the rise and fall of all of the parts of this data sculpture, Schneider has shown it may be possible to figure out where in the disease/recovery cycle a patient is.

The hope is eventually to be able to predict early on whether a patient is headed for recovery or not and, if not, how to best treat the patient based on where he or she is in the disease cycle.

"I think these sculptures show the cyclical nature of infections better than any graph I've been able to use previously," Schneider said. "But I still have to figure out how to publish these things. The journals always want flat pictures. We have to find a way to get around that."

Grant-writing, too. "The proposal formats often only let you submit a flat PDF. I've snuck movies into my PDFs in the past. But the granting agencies immediately banned doing that."

From 2013 through 2016, Schneider, who teaches year-round, began offering postdoctoral scholars and graduate students a 10-hour course in scientific animation. In spring 2017, Schneider switched to teaching similar classes, between quarters, in data sculpture. These classes, which are limited to a dozen students, typically attract as many as 50 applicants. The next one is in March.

Katharine Ng, PhD, a postdoctoral scholar in the Department of Bioengineering, has been Schneider's teaching assistant for both the scientific-animation and data-sculpture courses. "David's always open to new visualization techniques," she said. "He's always looking for ways to, first, convey science to lay audiences, and, second, force his fellow scientists to confront his data in a new way, hoping that maybe they'll catch some new aspect or perspective they might have otherwise overlooked." **ISM**

Diet

continued from page 1

was no.

"We've all heard stories of a friend who went on one diet — it worked great — and then another friend tried the same diet, and it didn't work at all," said Christopher Gardner, PhD, professor of medicine and the lead author of the study. "It's because we're all very different, and we're just starting to understand the reasons for this diversity. Maybe we shouldn't be asking what's the best diet, but what's the best diet for whom?"

Past research has shown that a range of factors, including genetics, insulin levels (which helps regulate glucose in the body) and the microbiome, might tip the scales when it comes to weight loss. The new study, published Feb. 20 in *JAMA*, homed in on genetics and insulin, seeking to discover if these nuances of biology would encourage an individual's body to favor a low-carbohydrate diet or a low-fat diet. The senior authors of the study are Gardner; Abby King, PhD, professor of health research and policy and of medicine; Manisha Desai, PhD, professor of medicine and of biomedical data science; and John Ioannidis, MD, DSc, professor of medicine.

A tale of two diets

In his quest to find out if individual biological factors dictate weight loss, Gardner recruited 609 participants between the ages of 18 and 50. About half were men and half were women. All were randomized into one of two dietary groups: low-carbohydrate or low-fat. Each group was instructed to maintain their diet for one year. (By the end of that year, about 20 percent of participants had dropped out of the study, due to outside circumstances, Gardner noted.)

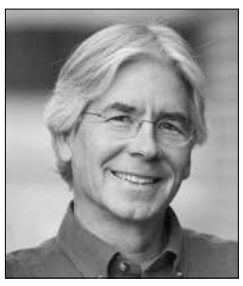
Individuals participated in two pre-study activities, the results of which were later tested as predictors of weight loss. Participants got part of their genome sequenced, allowing scientists to look for specific gene patterns associated with producing proteins that modify carbohydrate or fat metabolism. Then, participants took a baseline insulin test, in which they drank a shot of glucose (think corn syrup) on an empty stomach, and researchers measured their bodies' insulin outputs.

In the initial eight weeks of the study, participants were told to limit their daily carbohydrate or fat intake to just 20 grams, which is about what can be found in a 1½ slices of whole wheat bread or in a generous handful of nuts, respectively. After the second month, Gardner's team instructed the groups to make incremental small adjustments as needed, adding back 5-15 grams of fat or carbs gradually, aiming to reach a balance they believed they could maintain for the rest of their lives. At the end of the 12 months, those on a low-fat diet reported a daily average fat intake of 57 grams; those on low-carb ingested about 132 grams of carbohydrates per day. Those statistics pleased Gardner, given that average fat consumption for the participants before the study started was around 87 grams a day, and average carbohydrate intake was about 247 grams.

What's key, Gardner said, was emphasizing that these were healthy low-fat and low-carb diets: A soda might be low-fat, but it's certainly not healthy. Lard may be low-carb, but an avocado would be healthier. "We made sure to tell everybody, regardless of which diet they were on, to go to the farmer's market, and don't buy processed convenience food crap. Also, we advised them to diet in a way that didn't make them feel hungry or deprived — otherwise it's hard to maintain the diet in the long run," said Gardner. "We wanted them to choose a low-fat or low-carb diet plan that they could potentially follow forever, rather than a diet that they'd drop when the study ended."

Continuing to mine the data

Over the 12-month period, researchers tracked the progress of participants, logging information about weight, body composition, baseline insulin levels and how many grams of fat or carbohydrate they consumed daily. By the end of the study, individuals in the two groups had lost, on average, 13 pounds. There was still, however, immense weight loss variability among them; some dropped upward of 60 pounds, while others gained close to 15 or 20. But, contrary to the study hypotheses, Gardner found no associations between the genotype pattern or baseline insulin levels and a propensity to succeed on either diet.



Christopher Gardner

"This study closes the door on some questions — but it opens the door to others. We have gobs of data that we can use in secondary, exploratory studies," he said. Gardner and his team are continuing to delve into their databanks, now asking if the microbiome, epigenetics or a different gene expression pattern can clue them in to why there's such drastic variability between dieting individuals.

Perhaps the biggest takeaway from this study, Gardner said, is that the fundamental strategy for losing weight with either a low-fat or a low-carb approach is similar. Eat less sugar, less refined flour and as many vegetables as possible. Go for whole foods, whether that is a wheatberry salad or grass-fed beef. "On both sides, we heard from people who had lost the most weight that we had helped them change their relationship to food, and that now they were more thoughtful about how they ate," said Gardner.

Moving forward, he and his team will continue to analyze the reams of data collected during the yearlong study, and they hope to partner with scientists across Stanford to uncover keys to individual weight loss.

"I'm hoping that we can come up with signatures of sorts," he said. "I feel like we owe it to Americans to be smarter than to just say 'eat less.' I still think there is an opportunity to discover some personalization to it — now we just need to work on tying the pieces together."

The study's other Stanford co-authors are postdoctoral scholars John Trepanowski, PhD, and Michelle Hauser MD; research fellow Liana Del Gobbo; and senior biostatistician, Joseph Rigdon, PhD.

Gardner, Desai and Ioannidis are members of the Stanford Cancer Institute. Gardner and Ioannidis are members of the Stanford Cardiovascular Institute. Gardner and Desai are members of the Stanford Child Health Research Institute. Ioannidis is a member of Stanford Bio-X.

The study was funded by the National Institutes of Health, the Nutrition Science Initiative and Stanford's Clinical and Translational Science Award.

Stanford's departments of Medicine and of Health Research and Policy also supported the work. **ISM**

OF NOTE

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


Aijaz Ahmed


Alice Bertaina

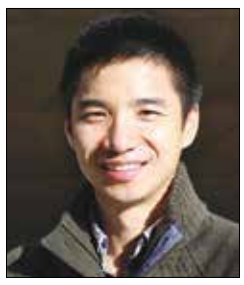

Mark Davis


Richard Frock


Jeffrey Glenn


Joo Ha Hwang


Nishita Kothary


Jonathan Long


Homero Rivas


Fatima Rodriguez

AIJAZ AHMED, MD, was promoted to professor of medicine, effective Jan. 1. He is the medical director of the adult liver transplant program at Stanford Health Care. His work focuses on outcomes research in liver transplantation, and database analysis and translational research on nonalcoholic fatty liver disease and viral hepatitis.

ALICE BERTAINA, MD, PhD, was appointed associate professor of pediatrics, effective Oct. 1. She specializes in the field of allogeneic hematopoietic stem cell transplantation in pediatric patients affected by blood malignancies and non-malignant disorders.

MARK DAVIS, PhD, professor of microbiology and immunology and the Burt and Marion Avery Family Professor, is leading a team that has received a $1.7 million Convergence 2.0 grant from Stand Up to Cancer. The funding will support the analysis of the immune systems of individuals who develop cancer versus those who do not, with the goal of finding predictive biomarkers of those most at risk.

RICHARD FROCK, PhD, was appointed assistant professor of radiation oncology, effective Jan. 1. His research interests include genome organization and editing, mechanisms of genomic instability, DNA double-strand break repair and chromosomal translocations.

JEFFREY GLENN, MD, PhD, was promoted to professor of medicine, effective Jan. 1. In addition, he was awarded a 2018 Harrington Scholar-Innovator Award. The awards, given by the Harrington Discovery Institute, aim to help early breakthroughs reach the clinic. Scholar-innovators receive $100,000, with an opportunity to qualify for up to $700,000, and can tap the expertise of a team of pharmaceutical industry specialists. Through the program, Glenn, who specializes in molecular virology, will work on the development of a broad-spectrum, single-dose therapeutic to treat the flu.

JOO HA HWANG, MD, PhD, was appointed professor of medicine, effective Jan. 1. He specializes in early detection and treatment of gastrointestinal malignancies, in particular using endoscopic submucosal dissection, endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography. His research investigates the use of focused ultrasound for enhancing drug delivery to pancreatic tumors.

NISHITA KOTHARY, MD, was promoted to professor of radiology, effective Dec. 1. Her clinical practice focuses on percutaneous and transarterial therapies for primary and metastatic liver cancer. Her research interests include radiogenomics and the use of advanced imaging for diagnosing and treating hepatocellular carcinoma.

JONATHAN LONG, PhD, was appointed assistant professor of pathology, effective Jan. 1. His group studies bioactive metabolite pathways that control mammalian metabolism and physiology. His research aims to discover new metabolite signaling pathways and to identify the enzymes, transporters and receptors that regulate the signaling.

HOMERO RIVAS, MD, was promoted to associate professor of surgery, effective Jan. 1. He specializes in minimal access surgery, and serves as the director of innovative surgery and the co-director of the fellowship in minimally invasive surgery. His research interests include digital health and telemedicine, as well as the use of wearable technologies in the operating room.

FATIMA RODRIGUEZ, MD, was appointed assistant professor of medicine, effective Jan. 1. Her research examines racial, ethnic and gender disparities in cardiovascular disease prevention and includes efforts to develop new interventions to address these disparities.

MIRABELA RUSU, PhD, was appointed assistant professor of radiology, effective Jan. 1. Her research focuses on developing analytic methods for biomedical data integration, with a particular interest in radiology-pathology fusion. She uses advanced machine learning and traditional data/image processing to create comprehensive, multiscale representations of biomedical processes and pathological conditions, allowing for in-depth characterization.

KATRIN SVENSSON, PhD, was appointed assistant professor of pathology, effective Jan. 1. Her research focuses on identifying and studying previously unknown hormones and their functions in order to understand the molecular pathways of metabolic disease and develop therapeutics.

DEAN WINSLOW, MD, professor of medicine, received a Society Citation Award from the Infectious Diseases Society of America. The honor recognized his "extensive knowledge, deep compassion and wide-ranging experience over more than four decades." In particular, he was recognized for his work with HIV drug resistance studies and his service as a flight surgeon in the military.

SAMUEL YANG, MD, associate professor of emergency medicine, was awarded a $3.8 million grant from the National Institute of Allergy and Infectious Diseases to fund a five-year project, in collaboration with Johns Hopkins University, that will investigate the use of single-cell microfluidic devices for the rapid diagnosis of bloodstream infections, which could improve patient outcomes and the use of antibiotics.


Mirabela Rusu


Katrin Svensson


Dean Winslow


Samuel Yang


Ke Yuan

KE YUAN, PhD, an instructor of pulmonary and critical care medicine, was named a 2017 Parker B. Francis Fellow. The fellowship provides $156,000 over three years to support the development of outstanding investigators beginning careers in pulmonary, critical care and sleep medicine. With her mentor, Mark Nicolls, MD, professor of pulmonary and critical care medicine, Yuan plans to investigate the role of pericytes, a cell in blood microvessels, in the pathobiology of pulmonary arterial hypertension. ISM

Rehearsal

continued from page 2

with a brain-machine interface got patterns of activity in the monkeys' brains into just the right spot, so they could carry out the same rotation task with their hands, even though they had never done so before.

A new way to probe the mind

"There are key differences between our paradigm and true mental rehearsal," Vyas said, and there are reasons to be cautious about interpreting the results too broadly. For one thing, one can't just ask a monkey to imagine ice skating, as one could with a person. For another, mentally rehearsing a task is not the same as using a brain-machine interface to do it. In the latter case, people get feedback on how they're doing, something they can only imagine in mental rehearsal.

"We can't prove the connection beyond a shadow of a doubt," Shenoy said, but "this is a major step in understanding what mental rehearsal may well be in all of us." The next steps, he and Vyas said, are to figure out how mental rehearsal relates to practice with a brain-machine interface — and how mental preparation, the key ingredient in transferring that practice to physical movements, relates to movement.

Meanwhile, Shenoy said, the results demonstrate the potential of an entirely new tool for studying the mind. "We used a brain-machine interface to probe and advance basic science, and that's just super exciting," Shenoy said.

Other Stanford co-authors are graduate student and Bio-X Bowes Fellow Nir Even-Chen; postdoctoral scholar Sergey Stavisky, PhD; Stephen Ryu, MD, an adjunct professor of electrical engineering; and Paul Nuyujukian, MD, PhD, an assistant professor of bioengineering and of neurosurgery.

Nuyujukian and Shenoy are members of Stanford Bio-X and the Stanford Neurosciences Institute.

The study was supported by the National Institutes of Health, the National Science Foundation, a Ric Weiland Stanford Graduate Fellowship, a Bio-X Bowes Fellowship, the ALS Association, the Defense Advanced Research Projects Agency, the Simons Foundation and the Howard Hughes Medical Institute.

Stanford's departments of Bioengineering and of Electrical Engineering also supported the work. ISM

Redesigned blog makes its debut

Scope, Stanford Medicine's award-winning blog, has unveiled a new design. It is mobile-friendly and features large images, improved navigation and enhanced accessibility for those with disabilities.

"After months of hard work, we're delighted to share it with the world," said Michelle Brandt, the director of digital media for the medical school's Office of Communication & Public Affairs and co-editor and co-founder of the blog. With a colleague, she spearheaded the blog's creation in 2009, when institutional blogs were relatively uncommon. Since then, Scope has gone on to win awards from the Association of American Medical Colleges and attract millions of readers. It has published nearly 9,000 posts.

The new design allows editors to showcase the blog's most newsworthy, and popular, stories. It also makes it easier for readers to share their favorite pieces on Twitter, Facebook, LinkedIn and Flipboard. The blog also has a Flipboard page — http://stan.md/2F1jPkB — and a new Medium page — https://medium.com/scope-stanford-medicine.

The blog publishes each weekday and features the latest news from Stanford Medicine; profiles of researchers and students; first-person accounts of life as a medical school student (the Stanford Medicine Unplugged series); live coverage of major events such as the Big Data in Precision Health Conference and Stanford Medicine X; podcasts featuring Paul Costello, the School of Medicine's chief communications officer (1:2:1); patient stories; and much more. ISM

SCOPE