INSIDE STANFORD MEDICINE

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Researchers have identifed existing drugs that can be used to treat symptoms of a rare eye disease.

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Procedure could benefit more stroke patients

By Bruce Goldman

STEVE FISCH / STANFORD HEALTH CARE

Gregory Albers is the principal investigator of a clinical trial that used software to identify stroke patients who could benefit from a clot-removal procedure, known as thrombectomy, after the window of time during which it generally has been considered effective has closed.

A 38-center clinical trial sponsored by the National Institutes of Health and led by researchers at the School of Medicine has shown that far more people than previously thought can benefit from an emergency procedure for acute ischemic stroke.

The improved outcomes were achieved through the use of brain-imaging software developed at Stanford. The software helps identify stroke patients who could benefit from a clot-removal procedure, known as thrombectomy, after the window of time during which it has generally been considered helpful has closed. Some patients showed dramatic improvement even when their brain clots were removed as long as 10 hours after the end of this six-hour window.

"Nearly half of all patients treated between six and 16 hours after the onset of their symptoms were largely spared from the consequences of their stroke," said the trial's principal investigator, Gregory Albers, MD, who is the Coyote Foundation Endowed Professor of Neurology and Neurological Science and the director of the Stanford Stroke Center.

Ischemic strokes account for about 85 percent of the roughly 750,000 strokes suffered annually in the United States. They occur when blood supply to part of the brain is cut off by a clot in a cerebral blood vessel. The resulting lack of oxygen and glucose quickly kills brain tissue in the immediate vicinity, and the affected area continues to expand until blood supply is restored.

'It saved my life'

On the night of April 23, 2017, Cindi Dodd, a 46-year-old graphic designer who lives in Salinas, California, went to bed around 10:30 p.m., anticipating a 5 a.m. wake-up from her husband, as she was scheduled for outpatient surgery at Stanford.

She did arrive at Stanford the next morning — not as an outpatient but as the victim of a massive ischemic stroke.

"My husband woke me up at 5 o'clock as planned, and when I started to speak to him I knew what I was trying to say in my mind, but it had nothing to do with the sounds that were coming out of my mouth," Dodd said. Her left side was paralyzed.

Her husband called 911. An ambulance arrived shortly afterward and rushed Dodd to Salinas Valley Memorial Hospital. But because she'd had the stroke while asleep, the "clock" determining whether she could be administered a clot-busting medication or undergo a thrombectomy had already started ticking. For stroke patients, the clock starts at the last time they're seen well, and for Dodd that was 10:30 p.m. the previous day. It was already too late for either of these treatments, the attending physicians explained.

But an emergency room physician told her husband about the ongoing Stanford trial and, with her husband's permission, called Stanford. Within 30-45 minutes, a helicopter operated by Stanford Health Care was on the scene to whisk Dodd to Stanford Hospital.

By the time Dodd's husband and high-school-age son, driving up from Salinas, had arrived at Stanford, she was already out of surgery. Seven days later she was discharged.

Almost fully recovered today after a combination of her thrombectomy, intensive rehabilitation and personal gumption — Dodd sports a tattoo reading, "I can, and I will" — she said, "I am literally standing on this Earth as a wife and a mother because of that procedure. It saved my life." She is talking, walking and driving as before, and will return to her full-time job in March.

See STROKE, page 7

Studying how chronic disease can lead to poor bone health, with an eye toward therapies

By Erin Digitale

COURTESY OF THE LEONARD LAB

Ryan Shih underwent a high-tech CT scan at the Stanford Assessment of Bone and Muscle Across the Ages Center, or SAMBA Center.

Kyla Kent had just finished conducting CT scans of bones in a 10-year-old boy's forearm and lower leg. Walking him back to the waiting room, she asked how he wanted to explain the images to his mom.

The detailed view provided by the CT machine, a high-resolution peripheral quantitative computed tomography scanner called XtremeCT II, is giving Stanford scientists unusually precise information about the toll of chronic diseases on children's bones. But young research participants are often more excited about the images' gee-whiz factor. Kent could sense the boy's mental wheels turning.

"Mom, here's what happened," the boy said. "From a single cell, a very small wizard was born. And he goes inside my arm — it doesn't hurt, I just felt a little pinch — and while he's in there, he takes a picture of the in-

See BONE, page 6

Positive attitude toward math predicts children's achievement in the subject

By Erin Digitale

PRESSMASTER / SHUTTERSTOCK.COM

For the first time, scientists have identified the brain pathway that links a positive attitude toward math to achievement in the subject.

In a study of elementary school students, researchers at the School of Medicine found that having a positive attitude about math was connected to better function of the hippocampus, an important memory center in the brain, during performance of arithmetic problems.

The findings were published online Jan. 24 in *Psychological Science*.

Educators have long observed higher math scores in children who show more interest in math and perceive themselves as being better at it. But it has not been clear if this attitude simply reflects other capacities, such as higher intelligence.

'Attitude is really important'

The new study found that, even once IQ and other confounding factors were accounted for, a positive attitude toward math still predicted which students had stronger math performance.

"Attitude is really important," said Lang Chen, PhD, the study's lead author and a postdoctoral scholar in psychiatry and behavioral sciences. "Based on our data, the unique contribution of positive attitude to math achievement is as large as the contribution from IQ."

The scientists had not expected the contribution of attitude to be so large, Chen said. The mechanism underlying its link to cognitive performance was also unexpected.

"It was really surprising to see that the link works through a very classical learning and memory system in the brain," said the study's senior author, Vinod Menon, PhD,

See MATH, page 7

Researchers find sleep improves with aid of incontinence drug

By Hanae Armitage

A drug used to curtail episodes of urinary incontinence in women also improves quality of sleep, a researcher at the School of Medicine reports.

People who experience urinary incontinence, especially at night, often have trouble maintaining normal sleep cycles. Now, the Stanford researcher sees promise in using one drug to help remedy both problems.

"Two of the biggest quality-of-life factors for older women are poor sleep quality and incontinence, and the older you get, the more prevalent both conditions are, and they do seem to be correlated," said Leslee Subak, MD, professor and chair of obstetrics and gynecology. "And so, if we can find a drug to treat one and effectively decrease the other too, that could be big for improving quality of life."

A paper describing the study was published Jan. 11 in *Obstetrics & Gynecology*. Subak is the senior author. Qurratul Ann Warsi, MD, a former clinical research scholar at the University of California-San Francisco, is the lead author.

In 2012, Subak, who was then on the faculty of UCSF, and her colleagues conducted a study called Bringing Simple Urge Incontinence Diagnosis and Treatment to Providers, or BRIDGES, which analyzed a specific drug's around-the-clock efficacy in curbing urgency incontinence, a condition characterized by a sudden urge to urinate and sometimes accidental leakage. The researchers conducted the study in women, as urgency incontinence is five to 10 times more common in women than it is in men.

MARCO SANCHEZ / UNIVERSITY OF CALIFORNIA-SAN FRANCISCO

Leslee Subak and her colleagues found that a drug that helps curb urinary incontinence can also help women sleep better.

The drug, fesoterodine, decreased accidental urination in study participants. The researchers also observed that it produced a handful of secondary beneficial effects, including less nighttime wakefulness caused by an urge to urinate.

Given the drug's success in diminishing urgency incontinence, including while sleeping, Subak followed up with a new question: Could this drug simultaneously help women catch extra shut-eye? Self-reported data from 645 female participants indicated that the answer was yes.

Two birds with one drug

In the initial 12-week BRIDGES study, Subak and her team recruited 645 female participants from 13 sites in the United States, whose average age was 56, and used a standardized evaluation of urgency incontinence to determine which participants would be best-suited for the trial. To qualify, participants had to indicate that they had experienced problems over the previous three months with accidental urination, occurring with a sudden urge to urinate.

Fesoterodine belongs to a larger class of drugs known as antimuscarinics. These agents help control accidental urination by blocking receptors in the bladder that, when activated, tell it to contract, a key physiological part of urination.

To determine if the drug also improved sleep quality, the researchers gave participants a standardized sleep evaluation, called the Pittsburgh Sleep Quality Index. The self-reported evaluation measures seven sleep-associated aspects, such as sleep duration, daytime sleepiness and how long it takes for an individual to fall asleep. Each category is scored on a scale from 0- 3; at the end, the score is tallied — the higher the score, the poorer the sleep quality. According to the Pittsburgh Sleep Quality Index, a score of 5 or more indicates poor sleep, and for the 57 percent of the cohort who reported poor sleep, the average score was a 6.4.

Women in the study recorded their baseline sleep patterns, the majority reporting that they were getting up one to two times per night to urinate. Those numbers may not seem bad on paper, but Subak said disrupting the sleep cycle more than once every night can start to take a toll.

"Getting up one time per night is acceptable for most people, but twice really starts to be disruptive and is associated with poorer quality of life and more daytime sleepiness," Subak said.

Women in the study who took the drug reported better sleep: Instead of having to empty their bladder once or twice a night, the group, on average, reported urinating just once per night, or not at all. Subak points out that finding a drug that can simultaneously address urinary incontinence and poor sleep is crucial for women, especially as they get older.

"As age increases, so do the prevalence and frequency of nighttime urination, and that especially poses risks for someone who is older," Subak said.

Thinking holistically

About a quarter of reproductive-age women, about half of menopausal women and about 80 percent of women who are 80 and older experience urgency incontinence. The older a woman is, the more dramatic the effect incontinence has on her quality of life.

Subak recalls a patient from the study telling her that incontinence doesn't kill you, but it takes your life away. "Patients might end up secluding themselves socially because they're worried about their bladder," she said. "But far worse, urinary incontinence is also one of the biggest factors for falling and fracturing for older women, especially those who have osteoporosis. That's why addressing 24-hour incontinence, especially in the geriatric population, is so critical."

Drugs such as fesoterodine empower physicians to think through the most well-rounded treatments for patients, Subak said, and there are many other similar pharmaceutical options that could work in the same way, too.

"It's a reminder to us as physicians to look at many co-morbid conditions that are synergistic. If an older person is saying 'I'm having trouble sleeping,' ask about nighttime urination; ask about urgency incontinence," Subak said. "It's important to look holistically at a patient, and especially at older women who have many of these problems co-existing. We have an opportunity to really look at how treating one can improve the others too."

Subak is a member of the Stanford Child Health Research Institute.

Researchers at the University of Utah, UCSF, University of Pennsylvania, University of Alabama-Birmingham, University of Iowa, University of Texas-Austin, Brown University, University of Tennessee Health Sciences Center, Harvard Medical School, Oregon Health Sciences University, University of Texas Health Science Center at San Antonio and California Pacific Medical Center Research Institute also contributed to the work.

The study was funded by an investigator-initiated award from Pfizer Inc. and by the National Institutes of Health.

Stanford's Department of Obstetrics and Gynecology also supported the work. ISM

Molecular imaging program launches interdisciplinary seminar series

The Molecular Imaging Program at Stanford is launching a new seminar series, IMAGinING THE FUTURE, aimed at encouraging interdisciplinary dialogue in medicine.

The series will feature national leaders in medicine, who will share their insights and stories of progress and scientific innovation.

The seminars, which are free and open to the public, will take place in Berg Hall at the School of Medicine's Li Ka Shing Center for Learning and Knowledge.

Douglas Lowy, MD, deputy director of the National Cancer Institute, will kick off the series at 1 p.m. Jan. 31 with a seminar on the role of precision medicine in cancer prevention and screening. A veteran of cancer research, Lowy has helped to make critical medical advances, including the development of human papillomavirus vaccines.

To register for the Jan. 31 seminar, visit https://www.onlineregistrationcenter.com/register/222/page1.asp?m=298&c=14. ISM

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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

New campuswide initiative to address Syrian refugee crisis

A team of Stanford researchers has launched an initiative to explore how universities can best respond to the large and growing number of Syrian refugees.

Based at the Stanford Center for Innovation in Global Health, the Stanford Refugee Research Project aims to create a campuswide collaborative of organizations and individuals committed to improving the health and well-being of the refugees and to identifying areas of need to direct coordinated relief efforts.

According to the United Nations refugee agency, the conflict in Syria is producing the largest number of refugees globally. The project team hopes to create a long-term model for university engagement with the Syrian refugee crisis, with the goal of expanding it to include other refugee populations.

"The number of refugees and internally displaced persons due to conflict is unprecedented," said Michele Barry, MD, director of the Stanford Center for Innovation in Global Health and principal investigator for the project. "We believe universities have an important role to play in better understanding the impact and limitations of current aid strategies."

Laila Soudi, a clinical research coordinator in psychiatry and behavioral sciences with experience working in Mideast refugee camps, is helping to lead the project, which was initiated last fall. The first phase engaged a team of student research ambassadors within each of Stanford's seven schools to identify key players within the university who are actively working in refugee relief efforts, or who are interested in getting involved. The results will be made available to the broader Stanford community in the spring.

Now in its second phase, the team recently returned from an exploratory trip to refugee camps and informal settlements in Lebanon and Jordan to assess the needs of Syrian refugees and meet with various relief agencies and organizations. The findings from this visit will inform the direction for implementing a pilot project in Lebanon or Jordan, or both, to improve refugee conditions with the help of Stanford students, faculty and staff.

The project is supported by a grant from the Stanford University Office of the President and School of Medicine Dean's Office. To get involved or learn more about refugee activities at Stanford, visit the project website at http://refugeeresearchproject.stanford.edu. ISM

Weight flux alters molecular profile of body systems, study says

By Hanae Armitage

The human body undergoes dramatic changes during even short periods of weight gain and loss, according to a study led by researchers at the School of Medicine.

As people pack on pounds or shed excess weight, they exhibit notable changes in their microbiome, cardiovascular system, immune system and levels of gene expression, the study found.

The researchers integrated a slew of "omics" profiling techniques to gather heaps of data revealing unique details of study participants' genomic, molecular, metabolic and bacterial composition. "Omics" is equivalent to tacking on "the study of" to the names of areas of biological inquiry. For example, "genomics" roughly translates to "the study of genes," and "proteomics" to "the study of proteins."

A paper describing the work was published online Jan. 17 in *Cell Systems*. The lead authors are Stanford postdoctoral scholars Wenyu Zhou, PhD, and Hannes Röst, PhD; staff scientist Kévin Contrepois, PhD; and former postdoctoral scholar Brian Piening, PhD. Senior authorship is shared by Michael Snyder, PhD, professor of genetics at Stanford; Tracey McLaughlin, MD, professor of medicine at Stanford; and George Weinstock, PhD, professor and director of microbial genomics at the Jackson Laboratory, an independent, nonprofit biomedical research institution.

"The goal here was to characterize what happens during weight gain and loss at a level that no one has ever done before," Snyder said. "We also really wanted to learn how prediabetic folks might differ in terms of their personal omics profiles and their molecular responses to weight fluctuation."

Snyder and his colleagues found that even with modest weight gain — about 6 pounds — the human body changed in dramatic fashion at the molecular level. Bacterial populations morphed, immune responses and inflammation flared, and molecular pathways associated with heart disease activated. But that's not the end of the story. When study participants lost the weight, most of the rest of the body's systems recalibrated back to their original states, the study found.

Snyder's lab has a particular interest in understanding weight change on the microscale among people who are insulin resistant, meaning their glucose-processing ability is compromised, because it's a common precursor to Type 2 diabetes. To that end, the study compared differences in baseline omics of insulin-resistant participants with those of healthy individuals. The researchers then looked at two major questions: How does weight gain affect omics profiles? And, what happens once that weight is lost?

'Billions of measurements'

The study included 23 participants. Thirteen were insulin-resistant, and 10 were insulin-sensitive, or able to process insulin normally; all had body mass indexes of between 25 and 35 kilograms per square meter. (A BMI of 25 is on the high-end of normal; a BMI of more than 40 roughly equates to morbid obesity). The researchers pooled information from each person's transcriptome, a collection of molecules that reveal patterns of DNA expression; proteome, the complete set of proteins an individual actively produces; microbiome; and genome.

"In the end, we literally made billions of measurements," said Snyder, who is the Stanford W. Ascherman, MD, FACS, Professor in Genetics.

At the outset of the study, Snyder and his team found notable baseline differences between the insulin-resistant and insulin-sensitive groups. Among disparities in protein production and microbial populations, Snyder spotted one big discrepancy: Molecular markers for inflammation were only found in the bloodstreams of insulin-resistant participants. Inflammation is a known issue in people with diabetes, and early omics profiling like this, Snyder said, could help flag inflammation-associated molecules in people who are not diabetic but at risk for the disease.

> "I didn't expect 30 days of overeating to change the whole heart pathway."

"In these analyses, we're looking at individual molecules that are changing, and then we're expanding them to the pathway level," Snyder said. The "pathway level" is equivalent to a system, like the immune or cardiovascular system. "So, when we find a molecule that seems out of whack, we then ask if it falls into any larger pathways in the body."

After looking for differences at baseline, the researchers changed up the parameters. The participants received a high-calorie diet, and after 30 days they had, on average, tacked on 6 pounds. And with weight gain — moderate though it was — omics profiles shifted too. Inflammation markers went up in both the insulin-resistant and healthy groups. In insulin-sensitive participants, a microbial population called *Akkermansia muciniphila*, which is known to protect against insulin resistance, shot up.

LEE ABEL

Michael Snyder and his colleagues took billions of measurements of 23 study participants and found that changes in weight resulted in dramatic, systemwide changes throughout their bodies.

But perhaps the most striking change was a shift in gene expression associated with increased risk for a type of heart failure called dilated cardiomyopathy, in which the heart cannot pump blood efficiently to the rest of the body, Snyder said.

"That was quite surprising. I didn't expect 30 days of overeating to change the whole heart pathway," he said. "But this all fits with how we think of the human body — it's a whole system, not just a few isolated components, so there are systemwide changes when people gain weight."

But Snyder said not to sweat the holiday heft just yet; there's good news too: Once the participants had dropped the excess weight, their microbes, molecules and gene-expression levels bounced back to their normal levels, for the most part.

Omics in the future of medicine

However, a small subset of weight-gain-associated shifts in protein and molecule production did persist, even after participants had shed the extra pounds, the study found. There's not enough evidence to draw concrete clinical conclusions, "but it is an indication that some of these effects could be longer-lasting," Snyder said. One thing to note, he continued, is that even though there were trends in omics shifts, each participant exhibited particular changes to his or her own specific omics profile — a nod to the importance of deep, integrative sequencing and data collection when diagnosing and treating patients with precision-health tools.

"Big data will be critical to the future of medicine, and things like these integrative omics profiles will offer an understanding of how the human body responds, in a very personal way, to different challenges," Snyder said. "I think it will be a critical part of managing human health in the future."

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

The study's other Stanford co-authors are postdoctoral scholars Gucci Jijuan Gu, PhD, Tejaswini Mishra, PhD, Imon Banerjee, PhD, Colleen Craig, PhD, Reza Sailani, PhD, Liang Liang, PhD, and Charles Abbott, PhD; research assistant Christine Yeh, MSc; research study coordinator Elizabeth Colbert; graduate researcher Cynthia Chen; former graduate student Kimberly Kukurba; research dietician Dalia Perelman, MS; software developer Denis Salins; genetic counselor Shannon Rego, MS; life science research professional Jessica Wheeler, MS; Daniel Rubin, MD, associate professor of biomedical data science, of radiology and of medicine; and Sharon Pitteri, PhD, assistant professor of radiology.

Snyder, McLaughlin, Rubin and Pitteri are members of Stanford Bio-X. Snyder and McLaughlin are members of the Stanford Child Health Research Institute. Snyder, Rubin and Pitteri are members of the Stanford Cancer Institute. Snyder and Rubin are members of the Stanford Neurosciences Institute. Snyder is a member of the Stanford Cardiovascular Institute.

Researchers at the Jackson Laboratory for Genomic Medicine, Yale University, the Royal Institute of Technology, the Chalmers Institute of Technology, the University of Gothenburg and Uppsala University also contributed to this work.

The study was funded by the National Institutes of Health, the American Diabetes Association, the Swiss National Science Foundation, the European Molecular Biology Organization, the Swedish Research Council and gifts from anonymous donors.

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

Three faculty members named National Academy of Inventors fellows

Three School of Medicine faculty members have been named fellows of the National Academy of Inventors.

Fellows are selected based on their "innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development and welfare of society," according to the academy.

The Stanford fellows are:

HELEN BLAU, PhD, the Donald E. and Delia B. Baxter Foundation Professor and a professor of microbiology and immunology. She directs the Baxter Laboratory for Stem Cell Biology. Her research has uncovered regulatory networks controlling nuclear reprogramming and therapeutic agents to enhance muscle regeneration in aging and dystrophy.

Helen Blau

Stanley Cohen

H. Tom Soh

STANLEY COHEN, MD, the Kwoh-Ting Li Professor and professor of genetics. His research helped spawn the revolution in genetic engineering. His lab currently studies mechanisms that affect the expression and decay of normal and abnormal mRNAs, and also RNA-related mechanisms that regulate microbial antibiotic resistance

H. TOM SOH, PhD, professor of radiology and of electrical engineering. He has devised sensors capable of continuously monitoring specific biomolecules in vivo and a control system for achieving real-time, closed-loop controlled drug delivery in live animals.

The new members will be inducted in a ceremony on April 5 in Washington, DC. ISM

5 QUESTIONS

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

On ranking drug companies' clinical trial reporting

Pharmaceutical companies have come under fire in recent years for failing to meet standards for reporting the results of clinical trials, but a new analysis by the nonprofit organization Bioethics International indicates that some companies are improving.

In December, Bioethics International published its second "Good Pharma Scorecard," which found that companies are making "meaningful progress" on some metrics, in BMJ Open. *The 2017 ranking evaluated clinical trial registration, results reporting, clinical study report synopsis sharing and journal article publication rates for new drugs approved by the Food and Drug Administration in 2014 that were sponsored by large drug companies. The FDA approved 19 novel new drugs sponsored by 11 large companies involving 553 trials that year.*

Two of 11 ranked companies — Johnson & Johnson and Sanofi — achieved the highest overall score for clinical trial transparency, both scoring 100 percent. AbbVie, Celgene, Merck, and Astra Zeneca all scored at or above the industry median.

Michelle Mello, JD, PhD, a Stanford professor of law and of medicine and a core faculty member at Stanford Health Policy, is a co-author of the report and a member of Bioethics International. She discussed the new findings with writer Beth Duff-Brown.

1 What are the main takeaways of this second scorecard?

MELLO: We found that companies are taking their legal obligations around clinical trial reporting seriously. There is high compliance with the reporting requirements of the federal FDA Amendments Act. We also found there are some emerging industry leaders that are going further than the law requires in getting patients and doctors the information they need — and there are clear opportunities for other companies to do more.

The 2017 scorecard shows progress within the industry on some measures since the first scorecard was released in 2015. We found that the proportion of new drugs for which all phase-2 and -3 trials that supported a new drug application were disclosed went up from 50 percent in the 2015 rankings to 67 percent this time. We also found that the public availability of results for trials conducted in patients for each drug went up from a median of 87 percent to 96 percent, measured at 13 months post-FDA approval.

2 Why is such a scorecard necessary?

MELLO: Disclosing complete information about clinical trials is important because it gives doctors, prescription drug formulary managers and others the information they need to make the best decisions concerning prescriptions and insurance coverage. Historically, not all trial results have been reported, creating a selective view of the evidence base for a drug.

National Institutes of Health policy now requires making information about all clinical trials available to alleviate public concerns about whether useful information is being hidden and speed up the decision-making based on safety signals. And disclosing information from phase-1 trials may help speed innovation and save money by preventing others from traveling down known, dead-end pathways or empowering them to design better trials based on the lessons learned from previous studies.

The scorecard is a way of reinforcing incentives for companies to provide this information. We conclude in our study, "Celebrating progress — and identifying where it is not occurring as quickly as it could — can move the field forward toward a shared vision of transparency and what it can achieve."

Michelle Mello

3 The first scorecard showed that nearly half of all drugs reviewed by the FDA in 2012 had at least one phase-2 or -3 study that was not published, and only 20 percent of final trial results were posted on the ClinicalTrials.gov registry. What do you think helped spur the reporting improvements since then?

MELLO: Companies' reporting has been monitored and publicized pretty widely — by our scorecard and by the NIH, among others. Through our project, we learned about some of the barriers to complete, timely reporting; for example, sometimes one company acquires another and the transition causes delays. But we also saw high levels of engagement in the issue; most companies are trying to get things right. There's still some disagreement, though, about the importance of reporting phase-1 trials, which are conducted in healthy participants rather than patients with an illness.

4 Polls routinely show that most Americans believe pharmaceutical companies are more concerned with profit than people. Is greater transparency about clinical trials likely to improve this situation?

MELLO: There are a number of issues that may have prompted this distrust — certainly, one issue that is very much in the spotlight at the moment is the high cost of prescription drugs. But much of this distrust dates to incidents many years ago in which it was discovered that companies incompletely reported clinical trial information, or in some cases distorted published analyses, and the drugs were later linked to safety problems. Following the old adage that sunlight is the best disinfectant, the transparency movement has been an effort to restore the public's confidence that pharmaceutical companies can conduct and report clinical research responsibly.

5 How does the scorecard process work?

MELLO: For new drugs approved by the FDA in a given year that were sponsored by the largest 20 pharmaceutical companies, a team of researchers scours FDA documents, nearly 40 clinical trial registries and medical journal articles, and then they match up drugs, clinical trials and public reports. We conduct this analysis for each trial, then each drug and finally each company. We create a company ranking based on all the drugs each had approved that year. And we work independently of companies, but give them a chance to review our results and methods to make sure we haven't missed anything. ISM

Medical school news office wins national awards

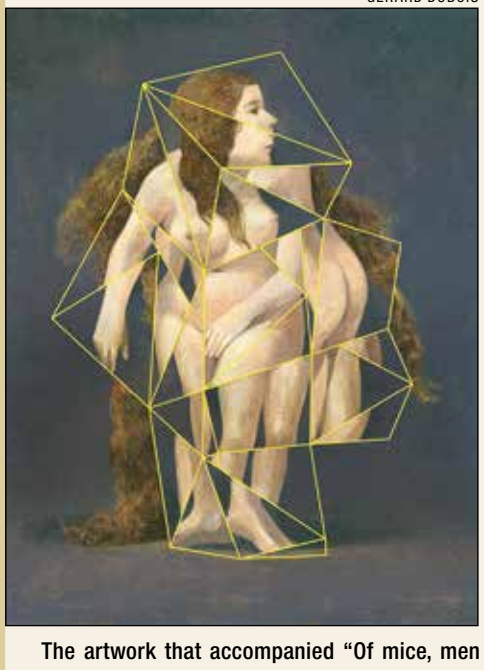
By Susan Ipaktchian

Writers and editors in the School of Medicine's Office of Communication & Public Affairs have received top awards for their work in the Association of American Medical Colleges' annual competition.

The office received a total of seven awards, including three golds in the contest's writing categories, for work published in 2016-17.

Science writer Krista Conger received the gold award in the basic-science writing category for "Of mice, men and women," which appeared in the spring 2017 issue of *Stanford Medicine* magazine. The story led off a themed package about sex, gender and medicine, and examines efforts to embrace and account for sex and gender differences in research. One judge noted that the story covers a critical topic in the world of biomedical research and that it was "presented clearly and creatively."

GÉRARD DUBOIS



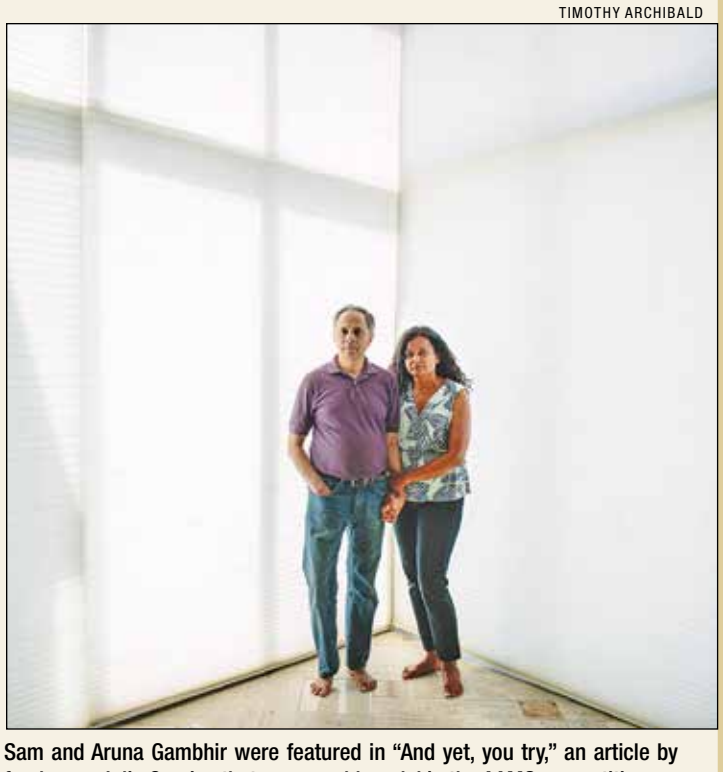
The artwork that accompanied "Of mice, men and women,"an article by Krista Conger that won a gold medal in the AAMC's annual competition.

Another story in that issue of the magazine earned a silver award in the same category: "Two minds," by science writer Bruce Goldman, explores the question of whether the brains of men and women are wired differently. "Fresh consideration of an essential topic in neuroscience, presented in a crisp, compelling article," one judge wrote.

"The puzzle solver," by science writer Tracie White, received the gold medal in the general staff writing category. Published in the spring 2016 issue of the magazine, the story describes a Stanford researcher's efforts to solve the biochemical puzzle of chronic fatigue syndrome, a disease afflicting the researcher's son. One judge said it was a "moving and emotional piece, which was well-conceived and designed."

In the solicited articles category, freelance writer Julie Greicius received the gold medal for "And yet, you try," published in the fall 2016 issue of *Stanford Medicine*. The feature describes the experiences of a Stanford diagnostics expert and his wife as they embarked on a quest to save their son after the teenager was diagnosed with a brain tumor. "This piece sensitively addresses the ultimate irony of a father trying to save a son afflicted with the very same aggressive brain cancer he studies," one judge wrote. "It is told with both sensitivity and a clear explanation of our current understanding of the disease and the research underway to address it. The family's courage shines through."

TIMOTHY ARCHIBALD



Sam and Aruna Gambhir were featured in "And yet, you try," an article by freelancer Julie Grecius that won a gold medal in the AAMC competition.

Stanford Medicine magazine earned a silver medal in the external publications category. Judges praised the look and the content of the magazine, describing it as well-written, artistic and informative. "I would call it the *New Yorker* or *The Atlantic* of medical school publications," one judge wrote. "Articles are insightful and passionately written." The magazine is edited by Rosanne Spector.

News releases written by members of the office also earned recognition. White received a silver medal for "Unroofing surgery relieves debilitating symptoms of heart anomaly." The judges praised the release for presenting straightforward information that was easily understandable for a variety of audiences.

And Goldman received an honorable mention in the news release category for "Study shows how slow breathing induces tranquility." Judges said the writing was effective and informative.

The office's news releases are edited by John Sanford.

The awards are given by the AAMC's Group on Institutional Advancement, which includes communications, development and alumni relations staff at academic medical centers. This year's awards will be presented March 22 at the group's annual meeting in Seattle. ISM

Pre-approved drugs used for treatment of rare eye disease

By Becky Bach

Demonstrating the potential of precision health, a team led by a researcher at the School of Medicine has matched existing drugs to errant proteins expressed by patients with a rare eye disease.

"Analyzing fluid samples from the eye can totally change how we treat patients," said Vinit Mahajan, MD, PhD, associate professor of ophthalmology.

Vinit Mahajan

The team employed proteomics, the large-scale study of proteins, in identifying four on-the-market drugs that successfully quelled symptoms triggered by several of the overabundant proteins. The findings, although not curative, demonstrate the potential of treating rare and complex eye conditions — and potentially other inflammatory diseases — by matching existing drugs with proteins that are abnormally expressed in the eyes of individual patients.

A paper describing the research was published online Dec. 21 in *JCI Insight*. Mahajan is the senior author. Gabriel Velez, an MD-PhD student at the University of Iowa and a visiting research scholar at Stanford, is the lead author.

"Patients with rare diseases often have few therapeutic options, and many conventional therapies fail them," Velez said. "Proteomic profiling allows for clinicians to analyze a patient's diseased tissue in real time and identify proteins that are targeted by already-approved drugs."

The genetic eye disease is called neovascular inflammatory vitreoretinopathy, or NIV. It is a progressive, inflammatory condition that evades all current therapies. Patients with the disease eventually go blind. It is exceptionally rare and only affects a handful of families worldwide, including an Iowa family studied and treated by Mahajan when he was at the University of Iowa. Initial symptoms, which include internal inflammation of the eye, cataract development and vision changes, usually appear when individuals are in their 20s. By the time patients are in their 50s and 60s, their vision has usually deteriorated into blindness, Mahajan said. Sometimes, eyes become so atrophied and painful they need to be removed.

Although a team led by Mahajan identified the gene responsible for the disease in 2012, a cure has yet to be developed. In the past, clinicians treating NIV patients used a trial-and-error approach to treat each symptom as it appeared, Mahajan said.

"This constant uphill battle to save the vision of NIV patients made us determined to find the molecules active inside the eye that can lead us to better therapies," Mahajan said.

Analyzing biopsies

Researchers performed liquid biopsies: A small amount of intraocular fluid was extracted from eight eyes of members of the same family at various stages of NIV and, as a control, four eyes with a noninflammatory eye disease. The researchers looked for 200 types of immune-signaling molecules called cytokines and identified 64 that were different, usually more abundant, in the eyes affected by NIV. In addition, they found that a protein called TNFalpha, which is usually abnormal in inflammatory conditions, was not elevated. Clinicians had previously assumed it was a culprit in NIV, yet infusions of an anti-TNFalpha drug called infliximab hadn't alleviated symptoms for patients with the disease. Now they know why.

"That's one of the important stories here," Mahajan said. "There's no target for the drug inside the eye, which totally explains why the drug didn't work. One of the benefits of this precision health approach is to identify which drugs we shouldn't use."

The researchers worked through the symptoms of the disease, matching each one with abnormal levels of proteins from the biopsies, and then with existing drugs that could potentially provide relief.

One feature of NIV is the excessive formation of new blood vessels in the retina, which can lead to a blinding hemorrhage. Clinicians traditionally treat this type of hemorrhage with surgery. However, eye surgery prompts inflammation and scarring in NIV patients. The protein analyses revealed elevated levels of vascular endothelial growth factor, or VEGF, that correlated with moderate cases of the disease. The researchers turned to an anti-VEGF drug, bevacizumab, which had been approved to treat macular degeneration. Injections of bevacizumab were able to resolve hemorrhages in seven NIV eyes without surgery, the study said.

Drug reduces eye inflammation

Another symptom of NIV is cellular inflammation and leakage of proteins into the eye, which patients experience as cloudy vision, akin to looking through a fog, with occasional "floaters" or shadows, Mahajan explained. Through the protein analysis, researchers spotted several abnormally expressed molecules that drive these inflammatory symptoms. The molecules help determine the fate of developing immune cells known as T cells. After reviewing existing drugs, the researchers decided to try injections of methotrexate, which targets T cells in arthritis. It successfully reduced the number of inflammatory cells in the eye, the study said.

The protein analysis also revealed numerous inflammatory compounds that could be treated with steroids, so the research team decided to put steroid implants into three of the NIV eyes. The implants, which release steroids continuously over two years, reduced levels of 31 molecules related to inflammation and the eye's abnormal immune response.

But the study participants eventually developed scarring around the implants, suggesting that some of the proteins contributing to inflammation weren't effectively blocked by steroids. And even after the steroid implantations, these eyes still expressed elevated levels of the inflammation-related protein interleukin-6.

The researchers used this clue to solve another issue in NIV: Scar tissue grows inside the eye, causing the retina to detach from the back of the eye. Surgery is the only option for treating this complication, but in NIV the scarring is so extensive the retina detaches again after the surgery. The researchers gave one participant in the study, who had already lost the use of one eye, a drug called tocilizumab to block interleukin-6 after reattaching her retina. The surgery was effective, marking the first time a retina has remained attached in an NIV patient and suggesting the drug may be beneficial to others with scarring inside the eye, Mahajan said.

> **"This is a fantastic example of the precision health approach we're taking in ophthalmology at Stanford."**

The researchers also used the protein analysis to supplement and confirm the classification of NIV into five stages of severity. Now, in addition to physical symptoms, they know which proteins are most active in each stage, Mahajan said. For future patients, a liquid biopsy from the eye could help provide more precise diagnoses, he said.

More gradual decline in eye health

"For the NIV patients in this family, the slope of their decline, once steep, is now more gradual. We're still working on a cure," Mahajan said. "But we can do a better job of trying to maintain their sight with what we've learned."

The applications of the approach are even broader, Mahajan said.

"In the future, we can imagine, in difficult-to-diagnose patients or patients not responding to treatment, just removing a few drops of fluid from the eye to very quickly learn exactly which proteins to target," he said. "Liquid eye biopsies are outpatient procedures that are safe and painless."

Mahajan said he believes the work illustrates the power of proteomics, which could help fulfill the potential of precision health to diagnose diseases before they advance and provide a real-time look at biochemical processes driving disease.

"This is a fantastic example of the precision health approach we're taking in ophthalmology at Stanford," said Jeffrey Goldberg, MD, PhD, professor and chair of ophthalmology. "It's innovative, has broad applicability and, most importantly, is helping patients."

Researchers at the University of Iowa and Columbia University also contributed to the study.

The research was funded by the National Institutes of Health; the Doris Duke Charitable Foundation; National Cancer Institute; Research to Prevent Blindness; the RD-Cure Consortium; the Tistou and Charlotte Kerstan Foundation; the Schneeweiss Stem Cell Fund; the state of New York; the Joel Hoffman Fund; the Professor Gertrude Rothschild Stem Cell Foundation; and the Gebroe Family Foundation.

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

Iowa woman, family members live with rare eye condition

By Becky Bach

Darlene Katzin considers herself lucky. After all, she's 74 and still has some sight, albeit limited, in her right eye.

Katzin is a member of what she calls "the blind family," a large, multigenerational Iowa family affected by a rare eye disease known as neovascular inflammatory vitreoretinopathy, or NIV. The disease stems from a mutation in the calpain-5 gene, which codes for an enzyme that breaks down proteins in some cells in the retina.

Katzin's mother went blind, as did her brother, cousins and dozens of other distant relatives. "I lived with blind people all my life. We knew what to expect," said Katzin, who lives in a small southeastern Iowa town with her boyfriend, Ed, and her dog, Tigger.

She began wearing glasses at 14 and has suffered from so many complications along the way she's lost track. As her vision slipped away, Katzin lost her driver's license and was forced to give up her job as a housekeeping manager in Pennsylvania and return to Iowa.

A correct diagnosis, at last

But she was never correctly diagnosed until she experienced a blinding hemorrhage more than a decade ago when she was in Iowa City for a college graduation.

"We went to eat at a sports bar, and I was looking at a TV and all of a sudden it was gone. I told my friend, 'My eye just hemorrhaged.'"

That emergency room visit, and the tests that followed, led to her diagnosis and her introduction to Vinit Mahajan, MD, PhD, who moved this year from the University of Iowa and is now an associate professor of ophthalmology at Stanford.

Katzin said she was glad to participate in his research, which she hopes will help others with conditions like hers.

It isn't an easy condition to live with. Katzin said she misses being able to drive and the independence a driver's license brings. "I don't like being dependent," she said, reflecting on the time it takes her friend to drive her to the eye clinic in Iowa City, or even to the local Walmart, where she tries to do all of her shopping to save trips.

But she's eager to emphasize that her plight isn't that bad.

When she bumps into people, she just explains that she's blind and couldn't see them. "I just laugh it off — it's no big deal," she said. She enjoys gardening and spending time with her dog and with family and friends.

"If you ask any of my blind relatives, life is good," Katzin said "Although we do not see, we still have our sense of humor. We still have our hearts of gold. We still enjoy life." ISM

COURTESY OF DARLENE KATZIN

Darlene Katzin (left) and several members of her family have an eye disease known as neovascular inflammatory vitreoretinopathy.

Bone

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side of my bone with his iPhone 6s camera!"

Kent, telling the story, stopped and chuckled. "I could not have come up with that explanation on my own," she said. Kent is the technical director of the Stanford Assessment of Bone and Muscle Across the Ages Center, or SAMBA Center, a multidisciplinary research effort to document and find ways to improve bone health over the life span.

ELENA ZHUKOVA / LUCILE PACKARD FOUNDATION FOR CHILDREN'S HEALTH

Mary Leonard studies how chronic childhood diseases, including diabetes, chronic kidney disease and cancer, take a silent toll on patients' bones.

The work, much of which focuses on kids, is led by Mary Leonard, MD, professor of pediatrics and of medicine and the center's founding director. Many chronic childhood diseases, including diabetes, chronic kidney disease, inflammatory bowel disease, congenital heart defects and childhood cancer, take a silent toll on patients' bones. Leonard and her team want to help patients maximize their bone health in childhood and reduce their risk for osteoporosis later on.

'A critical period'

"Childhood and adolescence is a critical period for building a big, strong, healthy skeleton," said Leonard, who holds the Arline and Pete Harman Professorship for the Chair of the Department of Pediatrics. Healthy children and teens have a unique opportunity to build a bulwark of bone mass to prevent osteoporosis later in life, she said. Throughout childhood, and especially during the growth spurt of puberty, the bones are constantly being reshaped by the interplay of two types of bone cells: osteoclasts, which chew up existing bone, and osteoblasts, which build new bone and mineralize it with plenty of calcium and phosphorus. In healthy kids, many different physiological factors — including diet, weight-bearing exercise and the activity of various hormones — affect the bone-modeling process, shaping how big and heavy the bones become.

"The flip side is that in chronic disease, we think there's a window during development when kids' bones are especially vulnerable," Leonard said. Chronic disease can hurt adults' bones, too, but for children who are supposed to be building enough bone to last a lifetime, the effects can be especially severe. "And once you stop growing, there's little opportunity to make the bones thicker," Leonard said. "That ship has sailed."

As experts at Lucile Packard Children's Hospital Stanford and other institutions develop new ways to help children survive previously life-shortening illnesses, long-term damage to kids' bones becomes more important to address. "We need to shift focus to health across the life span," Leonard said.

A powerful scanner

One key tool in Leonard's efforts to do that is the SAMBA Center's high-resolution CT scanner, the only such machine west of Missouri. It is designed to provide an extremely detailed view of the bone structure inside the arms and legs, and it uses much less radiation than a typical medical CT scanner.

"High-resolution CT scans help us understand why the bones are weak," Leonard said. "Is it because the shell of the bone is thin? Is it not dense enough? Does it have pores or holes it shouldn't have?" These details are telling: Inflammation leaves one type of damage traced on the bone, steroid medications leave another. Vitamin D deficiency looks different, too. "If we understand the underpinnings of the fragility, it gives us insight into the mechanism of bone damage," she said.

The high-resolution CT is such a new tool that the Stanford team had to begin by creating a normative database of bone scans from healthy children, a process that is still underway. They are also collaborating with other scientists around the world to agree on standardized methods for running the scans.

Once the high-resolution CT data is collected, it's studied using finite element analysis, a technique borrowed from engineering physics. "We treat the bone like it's a bridge or airplane wing and see: What is the failure load?" Kent said. Two children with the same bone density may not have the same functional level of weakness in their bones; high-resolution CT can distinguish between them.

"We don't do these scans to predict fractures in children; we do it because we want to understand what their disease is doing. It helps us think more about different treatment options," Leonard said.

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.

The team is also using more traditional methods of assessing bone health, including dual X-ray absorptiometry, or DXA, scans, which provide information about children's overall bone mass, lean body mass and body composition, as well as hand-grip testing, leg-endurance testing and maximum force generation tests, which measure different elements of limb strength to allow the team to assess how bones and muscles function as a unit.

COURTESY OF THE LEONARD LAB

Linnea Holm used a dynamometer at the SAMBA Center to test the strength of muscles in her lower leg and ankle region. Data from the machine helps researchers determine how muscles may affect the strength and quality of bones.

In healthy kids, bones and muscles work together to prompt the bone to grow, Leonard explained. "Your bone is listening: 'You're putting me under stress; I can sense the forces and I'll respond by getting stronger,'" she said. "When children are bedridden, they can lose a lot of bone mass because the signaling process isn't occurring. And in many chronic diseases, the patients who have the worst muscle mass also have smaller bones — not just less dense, actually smaller."

Putting bone discoveries to use

Bone health discoveries are already strengthening some patients' bones.

For instance, new medications for inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, now allow doctors to avoid treating kids with drugs that damage their bones. "These kids used to get treated with high doses of prednisone," Leonard said. "They had terrible skeletal fragility." The steroids led to vertebral compression fractures, injuries more typically seen in elderly osteoporosis patients. Now, doctors can instead prescribe biologics that selectively suppress gut inflammation and directly block the inflammatory molecules that damage bone.

Not only are the patients better off, the new treatments are helping researchers tease apart how much bone damage is caused by steroids and how much by the disease itself, since inflammation also damages bone. Leonard co-authored a recent series of studies demonstrating that children and adolescents with Crohn's disease have remarkable improvements in growth, muscle mass and bone density and size after treatment with biologics. "These patients have made the most progress because treatments for the disease have improved so much," Leonard said.

For other chronic diseases, there's farther to go. In the 25 years Leonard spent at the Children's Hospital of Philadelphia before moving to Stanford in 2014, much of her research was devoted to understanding bone damage in children with chronic kidney disease. Metabolism of the bone-building hormone vitamin D is regulated by the kidney: When the kidneys don't work, a complex cascade of calcium and phosphorus regulation gets thrown off and damages the bones. Leonard and her colleagues have shown that children with kidney disease have thin bones with low density and increased risk of fracture.

Today, Leonard's team is using both DXA scanning and their high-resolution CT scanner to get a more detailed view of these patients' bones.

"I think it will be really interesting to see how different their bone microarchitecture will be compared with the healthy controls we're also scanning," said Candice Sheldon, MD, a clinical fellow in pediatric nephrology whom Leonard is mentoring.

Looking ahead

Chronic kidney disease patients tend to be shorter than average, Sheldon said. Although growth-hormone and vitamin D supplementation are already used to help promote growth and protect these patients' bones, they are still more likely to break bones than healthy kids. "We still haven't figured out how to optimize therapy so these kids are as close to their healthy counterparts as possible," Sheldon said. She hopes the CT scans will give clues as to the exact mechanism of bone damage that will put the team on the trail of better therapies.

The team also hopes to understand how receiving a kidney transplant affects children's bones. After transplant, how much do the bones recover? Packard Children's has the largest pediatric kidney transplantation program in the country and spearheaded the development of steroid-free immunosuppression regimens in children. This is the ideal place to determine if bone density, structure and strength can recover following kidney transplant in children and adolescents.

In the future, Leonard hopes to investigate the long-term impact on bones of a new form of bone-marrow transplantation being developed at Stanford for certain cancer patients. Radiation therapy that is traditionally used to prepare patients for bone-marrow transplant also damages their bones, leaving childhood cancer survivors who have received the transplants with low bone density, low muscle mass and high body fat over the long run.

But a Stanford team led by Judith Shizuru, MD, PhD, professor of medicine and of pediatrics, and Maria Grazia Roncarolo, MD, professor of pediatrics and of medicine, is developing an antibody-based method of preparing patients for bone-marrow transplant that is intended to allow them to skip radiation.

"They're the first to do a stem cell transplant that doesn't require radiation, and we'll have an opportunity to see if this incredible new therapy prevents fractures in these patients," Leonard said.

Her team hopes their discoveries will translate into better ways to keep kids' bones strong for decades to come. "Bone fractures are painful, and the young patients we're studying are already dealing with so many other medical problems," said Sheldon. "Ultimately, we want to strengthen their bones so they can be happier and more active in childhood and throughout their adult lives as well." **ISM**

MIT's Aviv Regev to present annual McCormick Lecture Feb. 1

Computational and systems biologist Aviv Regev, PhD, will give the 2018 Katharine D. McCormick Distinguished Lecture at 4 p.m. Feb. 1 at the Li Ka Shing Center for Learning and Knowledge

The title of her talk will be "Reconstructing circuits — the power of random." The event is free and open to members of the Stanford community. A reception will follow. The deadline to register is 7 p.m. Jan. 31.

Aviv Regev

A professor of biology at MIT, Regev is also a Howard Hughes Medical Institute investigator, director of Klarman Cell Observatory at the Broad Institute and chair of the Broad Institute's faculty.

Regev and her colleagues develop experimental and computational approaches to decipher the mechanisms that underlie the transcriptional regulatory circuits in organisms ranging from yeast to humans. Members of her lab study how these transcriptional circuits change on a variety of timescales, from hours to millions of years. These studies yield detailed reconstructions and highlight key principles that govern the emergence of novel functions in gene regulation.

The lectureship is named for Katharine Dexter McCormick, a biologist and feminist who left a large bequest to Stanford with the hope that it would be used "in aid of women students attending the School of Medicine and more generally for the encouragement and assistance of women in pursuing the study of medicine, in teaching medicine and engaging in medical research." **ISM**

Math

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professor of psychiatry and behavioral sciences. Researchers had previously hypothesized that the brain's reward centers might drive the link between attitude and achievement — perhaps children with better attitudes were better at math because they found it more rewarding or motivating. "Instead, we saw that if you have a strong interest and self-perceived ability in math, it results in enhanced memory and more efficient engagement of the brain's problem-solving capacities," Menon said.

The researchers administered standard questionnaires to 240 children ages 7 to 10, assessing demographics, IQ, reading ability and working-memory capacity. The children's level of math achievement was measured with tests of their knowledge of arithmetic facts and ability to solve math word problems. Parents or guardians answered surveys about the children's behavioral and emotional characteristics, as well as their anxiety about math and general anxiety. Children also answered a survey that assessed their attitude toward math, including questions about interest in math and self-perceived math ability, as well as their attitude toward academics in general.

Forty-seven children from the group also participated in MRI brain scans while performing arithmetic problems. Tests were conducted outside the MRI scanner to discern which problem-solving strategies they used. An independent group of 28 children also was given MRI scans and other assessments in an attempt to replicate the findings from the cohort previously given brain scans.

Opening the door

Math performance correlated with a positive attitude toward math even after statistically controlling for IQ, working memory, math anxiety, general anxiety and general attitude toward academics, the study found. Children with poor attitudes toward math rarely performed well in the subject, while those with strongly positive attitudes had a range of math achievement.

"A positive attitude opens the door for children to do well but does not guarantee that they will; that depends on other factors as well," Chen said.

From the brain-imaging results, the scientists found that, when a child was solving a math problem, his or her positive-attitude scores correlated with activation in the hippocampus, an important memory and learning center in the brain. Activity in the brain's reward centers, including the amygdala and the ventral striatum, was not linked to a positive attitude toward math. Statistical modeling of the brain imaging results suggested that the hippocampus mediates the link between positive attitude and efficient retrieval of facts from memory, which in turn is associated with better problem-solving abilities.

"Having a positive attitude acts directly on your memory and learning system," Chen said. "I think that's really important and interesting."

The study could not disentangle the extent to which a positive attitude came from a child's prior success in math. "We think the relationship between positive attitude and math achievement is mutual, bi-directional," Chen said. "We think it's like bootstrapping: A good attitude opens the door to high achievement, which means you then have a better attitude, getting you into a good circle of learning. And it can probably go the other way and be a vicious circle, too."

STEVE FISCH

Vinod Menon is the senior author of a study that found that kids with a positive attitude toward math performed better in the subject.

The findings may provide a new avenue for improving academic performance and learning in children who are struggling, Menon said, cautioning that this idea still needs to be tested through active interventions.

"Typically, we focus on skill-learning in individual academic domains, but our new work suggests that looking at children's beliefs about a subject and their self-perceived abilities might provide another inroad to maximizing learning," Menon said. The findings also offer a potential explanation for how a particularly passionate teacher can nurture students' interest and learning capacities for a subject, he added. Inspiring teachers may be instinctively sharing their own interest, as well as instilling students in the belief that they can be good at the subject, building a positive attitude even if the student did not have it before.

Other Stanford authors of the paper are former research assistant Se Ri Bae; research scientists Shaozheng Qin, PhD, and Tianwen Chen, PhD; and former postdoctoral scholars Christian Battista, PhD, and Tanya Evans, PhD.

Menon is a member of Stanford's Child Health Research Institute, Stanford Bio-X and the Stanford Neurosciences Institute. The research was funded by the National Institutes of Health.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. **ISM**

Stroke

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"These astounding results will have an immediate impact in the clinic and will help us save many lives," Walter Koroshetz, MD, director of the National Institute of Neurological Disorders and Stroke, said in an NIH news release. "I really cannot overstate the size of this effect."

Results of the trial were published online Jan. 24 in *The New England Journal of Medicine* to coincide with Albers' presentation of the results at the American Heart Association's International Stroke Conference in Los Angeles.

The AHA has issued new acute-stroke treatment guidelines that reflect what the study found.

Key to the study's findings is a growing understanding that different individuals' strokes spread through brain tissue at different rates, Albers said. It's not so much the amount of time elapsed since a stroke began as the amount of remaining at-risk but salvageable brain tissue that determines who will benefit from stroke therapy, he said.

The investigators used the brain-imaging software to rapidly evaluate blood-flow data generated from incoming patients. Albers developed the software about a decade ago with study co-author Roland Bammer, PhD, then an associate professor of radiology at Stanford and now a professor at the University of Melbourne in Australia, and software engineer Matus Straka, PhD, who was then a senior scientist at Stanford.

Cagelike stent

Thrombectomy involves guiding a cagelike stent through the circulatory system to the site of an acute-stroke patient's brain clot, where the stent then encases the clot and physically extracts it.

"I really cannot overstate the size of this effect."

The procedure is currently recommended only for patients who reach a treatment center within six hours of a stroke. As many as 35 to 40 percent of all strokes occur during sleep, so the short window of time severely limits the number of stroke patients getting this procedure. Another treatment, intravenous injection of a clot-dissolving substance, has an even tighter AHA-recommended time limit for efficacy — 4.5 hours — and isn't very effective for treating large clots.

In the trial, patients were evaluated at treatment centers between six and 16 hours after incurring strokes originating in either of two large arteries in the brain: the middle cerebral artery or the internal carotid artery, which together account for about 25 percent of all strokes and the majority of severely disabling strokes. Patients age 90 or younger whose brains showed evidence of substantial amounts of at-risk but salvageable tissue were randomized into two groups: One set of patients, the intervention group, received thrombectomies. The others, the control group, received standard medical therapy.

Among the patients entered into the study, those who received a thrombectomy had far superior outcomes compared with those who didn't.

Patient selection matters

Patients were followed for 90 days after their strokes. (After this time period, stroke patients typically experience little additional recovery.) By 90 days, 26 percent of the patients in the control group had died and 16 percent had devastating disability. In contrast, only 14 percent of the thrombectomized patients had died, and 8 percent had severe disability. The combined plunge in these feared outcomes, from 42 percent of patients to 22 percent, represents the biggest improvement seen in any stroke-treatment trial to date, said Albers.

There was a slight, statistically insignificant increase in bleeding from the spot in the brain where the clot had been extracted. But this effect was dwarfed by the overall reduction in death and disability among those treated.

Albers noted one caveat: "Our trial's excellent results reflect our selection of patients most likely to benefit," he said. "Only about half of the patients we screened with the brain-imaging software had enough salvageable brain tissue to enter the study. For the others, the procedure was considered unlikely to be effective."

As a result of the trial's findings, which confirm and expand on a recently published large clinical trial using the same software to inform treatment decision-making, thrombectomy procedures for late-arriving patients will probably double, said Albers, and this also opens up the prospect of using clot-busting medications well beyond the current 4.5-hour window.

"It used to be that by five or six hours after a stroke, we had to say 'I'm so sorry, you arrived too late to be treated,'" he said. "But this is a new world."

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.

Albers is a member of the Stanford Neurosciences Institute.

Michael Marks, MD, professor of radiology, was the co-principal investigator of the trial, and Maartin Landsberg, MD, PhD, associate professor of neurology and neurological sciences, was the protocol director.Other Stanford co-authors of the study are clinical research manager Stephanie Kemp; senior research scientists Soren Christensen, PhD, and Michael Mlynash, MD; former postdoctoral scholar Jenny Tsai, MD, now at the Cleveland Clinic; clinical assistant professor of neurology Jeremy Heit, MD, PhD; associate professor of radiology Greg Zaharchuk, MD; PhD; and emeritus professor of biomedical data science Philip Lavori, PhD.

The trial was funded by the NIH.

Albers holds equity in iSchemaView, a company based in Redwood City, California, that has licensed the software from Stanford's Office of Technology Licensing. He is also a consultant for iSchemaView, which supplied the software used in the trial.

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

Psychiatry investigators awarded NIH grant to study autism

Three Stanford psychiatry investigators have been awarded a five-year, $2.5 million grant to study autism.

The researchers will work with University of California-Davis investigators as part of a new National Institute of Health Autism Center of Excellence.

Joachim Hallmayer, MD, professor of psychiatry and behavioral sciences; Ruth O'Hara, PhD, associate professor of psychiatry and behavioral sciences; and Sundari Chetty, PhD, instructor of psychiatry and behavioral sciences, will collaborate with autism expert David Amaral, MD, and his team at the UC-Davis MIND Institute.

The Stanford researchers will lead a project in which induced pluripotent stem cells, or iPS cells, are produced from children with autism who also have enlarged brains, or megalencephaly. The goal is to see whether brain cells derived from the iPS cells can provide any clues about what's causing the megalencephaly.

The work may also provide insights into potential treatment targets for kids with this form of autism. **ISM**

Irving Weissman receives several awards, honorary doctorate

Irving Weissman, MD, professor of pathology and of developmental biology, received several awards and an honorary doctorate in 2017.


Irving Weissman

He received the 2017 Donald Metcalf Award from the International Society for Experimental Hematology. The award recognizes distinguished society members who have made outstanding contributions to the field of experimental hematology.

Weissman, who holds the Virginia and D.K. Ludwig Professorship for Clinical Innovation in Cancer Research, also received a 2017 National Cancer Institute Outstanding Investigator Award, which recognizes accomplished leaders in cancer research and provides up to $600,000 a year for seven years. He plans to use the award to investigate whether mutations accumulate in a central nervous system stem cell clone that becomes a brain cancer stem cell.

He was awarded the 2017 Karl Landsteiner Memorial Award and Lectureship by the American Association of Blood Banking. The honor recognizes a scientist who has an international reputation in transfusion medicine or cellular therapies. Weissman was recognized for his pioneering role identifying and isolating the first hematopoietic stem cells in mice and humans.

He was awarded the Helmholtz International Fellow Award from the Helmholtz Association. The prize includes 20,000 euros (about $24,000) and an invitation to conduct research at one of the Helmholtz Centres. The Helmholtz Association of German Research Centres, funded by the German government, conducts research related to challenges facing society in several fields, including health.

In addition, he received an honorary doctorate from the Faculty of Medicine at the University of Turku in Finland. **ISM**

OF NOTE

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

CHARLES K.F. CHAN, PhD, was appointed assistant professor of surgery, effective Nov. 1. His group is investigating how stem cell niches change during tissue regeneration and aging and in diseases such as cancer.

HOWARD CHANG, MD, PhD, professor of dermatology and the Virginia and D.K. Ludwig Professor of Cancer Genomics, will receive the 2018 National Academy of Sciences Award in Molecular Biology. The $25,000 award honors a young scientist who has made a recent notable discovery. He was recognized for his "insightful discoveries of long noncoding RNAs and technologies unveiling the noncoding genome."

JONATHAN CHEN, MD, PhD, was appointed assistant professor of medicine, effective Nov. 1. His research focuses on mining clinical data sources to inform medical decision-making.

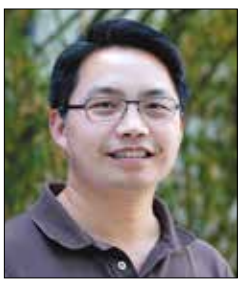
MICHAEL CHERRY, PhD, professor of genetics, has been awarded a $1.2 million grant as part of the National Institutes of Health Data Commons Pilot Phase. The four-year pilot project will explore how to make digital information available on collaborative platforms. With other investigators, he is responsible for the Alliance of Genome Resources data set, which will serve as a test case for the pilot project.

RONALD DALMAN, MD, the Walter Clifford Chidester and Elsa Rooney Chidester Professor of Surgery, was elected to a three-year term on the board of governors of the American College of Surgeons representing the Society for Vascular Surgery. With more than 80,000 members, the American College of Surgeons is the world's largest organization of surgeons.

LANE DONNELLY, MD, was appointed professor of radiology, effective Nov. 1. His work focuses on quality and patient safety in pediatric radiology. He is the chief quality officer at Lucile Packard Children's Hospital Stanford.

AARON GITLER, PhD, professor of genetics, was awarded the 2017 Friedrich Merz Guest Professorship at Goethe University Frankfurt. The honor, which includes $20,000 euros (about $24,000) and travel to Germany, was created to invite a highly respected scientist in pharmaceuticals or medicine to travel to the university to share his or her research and network with local researchers. Gitler was selected for his work in mice that halted the progression of the motor neuron disease amyotrophic lateral sclerosis (also known as Lou Gehrig's disease) for more than a year.


Charles K.F. Chan


Howard Chang


Jonathan Chen


Michael Cherry

ROBERT HARRINGTON, MD, professor and chair of medicine and the Arthur L. Bloomfield Professor, was awarded the Clinical Research Prize for 2017 from the American Heart Association. He was recognized for outstanding achievement in clinical cardiovascular science. He designs and leads clinical trials to improve care for patients with coronary heart disease, with a particular focus on reducing complications from blood clots.

SIDDHARTHA JAISWAL, MD, PhD, was appointed assistant professor of pathology, effective Nov. 1. His research focuses on the biology and clinical impact of somatic mutations in hematopoietic stem cells that arise during aging.

WILLIAM KUO, MD, was promoted to professor of radiology, effective Nov. 1. His research focuses on advanced vena cava filter retrieval; catheter-directed therapy for acute pulmonary embolism; and inferior vena cava, or IVC, filter outcomes. He directs the Stanford IVC Filter Clinic, the interventional radiology fellowship program and the integrated interventional radiology-diagnostic radiology residency program.

GRACE M. LEE, MD, was appointed professor of pediatrics, effective Nov. 1. Her work focuses on developing quality metrics for use in pediatrics, evaluating the impact of payment policies on health outcomes, preventing health care-associated infections and conducting near real-time surveillance to monitor the safety of medical product use.

TRACEY MCLAUGHLIN, MD, was promoted to professor of medicine, effective Sept. 1. Her research focuses on obesity, insulin resistance, diabetes and cardiovascular disease. She is a co-founder of the diabetes task force at Stanford Health Care.

JOHN MORTON, MD, associate professor of surgery, was named clinical editor of the *Bariatric Times*. He is the chief of bariatric and minimally invasive surgery and directs the bariatric and minimally invasive surgery fellowship at Stanford.

MINDIE NGUYEN, MD, was promoted to professor of medicine, effective Nov. 1. Her research focuses on the epidemiology and treatment outcomes of liver cancer, chronic hepatitis B and C and nonalcoholic fatty liver diseases. She is the hepatology clerkship director and the director for the hepatology fellowship.

JON PARK, MD, was promoted to professor of neurosurgery, effective Oct. 1. Clinically, he specializes in minimally-invasive spine surgery. His research focuses on nonfusion dynamic spinal stabilization and on both artificial disc and regenerative spinal technologies.

CAROLYN RODRIGUEZ, MD, PhD, assistant professor of psychiatry and behavioral sciences, has received an Eva King Killam Award from the American College of Neuropsychopharmacology. The honor recognizes an early career researcher who has made outstanding contributions to translational research in neuropsychopharmacology. She was recognized for her work investigating the role of glutamatergic pathways in obsessive-compulsive disorder.

JOSHUA SALOMON, PhD, was appointed professor of medicine, effective Aug. 1. His research focuses on priority-setting in U.S. and global health policy, including measurement and valuation of health outcomes, modeling patterns and trends in major causes of death and disability, and on evaluation of health interventions and policies. He directs the Prevention Policy Modeling Lab, a multi-institution research consortium that conducts health and economic modeling related to infectious disease.

ABRAHAM VERGHESE, MD, professor of medicine and the Linda R. Meier and Joan F. Lane Provostial Professor, received the Jonathan E. Rhoads Commemorative Lecture & Award from the American Philosophical Society, the College of Physicians of Philadelphia and the Hospital of the University of Pennsylvania Department of Surgery. His lecture highlighted physicians such as Che Guevara and Frantz Fanon whose medical conscience puts them in conflict with those in power. Verghese is an internist and medical educator whose interests include the patient-physician relationship and the bedside exam. **ISM**


Ronald Dalman


Lane Donnelly


Aaron Gitler


Robert Harrington


Siddhartha Jaiswal


William Kuo


Grace Lee


Tracey McLaughlin

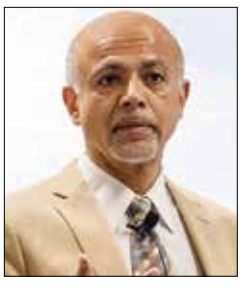

John Morton


Mindie Nguyen


Jon Park


Carolyn Rodriguez


Joshua Salomon


Abraham Verghese