INSIDE STANFORD MEDICINE

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A nutrition scientist busts myths about milk.
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Cells often destroyed in a wave of death

By Hanae Armitage

Inside a cell, death often occurs like the wave at a baseball game.

What starts with two hands flung skyward prompts another, and another, until the wave has rippled far and wide across the whole stadium. This kind of a rolling surge, spurred by the activity of one or a few things, is known as a trigger wave. A new study out of the School of Medicine has found that this phenomenon guides one of the most well-known and widespread forms of cell death: apoptosis.

PAUL SAKUMA

James Ferrell is the senior author of a paper that describes how trigger waves help guide a widespread form of cell death known as apoptosis.

It's not the first time trigger waves have been identified in the microcosms of life. The cell cycle, a cornerstone of cell biology in which cells divide to make new cells, regulates production via trigger waves, too. So do neuronal action potentials, which allow neurons to pass signals via electrical impulse. And it likely doesn't end there.

"This work is another example of how nature makes use of these trigger waves — things that most biologists have never heard of — over and over again," said James Ferrell, MD, PhD, professor of chemical and systems biology and of biochemistry at Stanford. "It is a recurring theme in cell regulation. I bet we'll start to see it in textbooks soon."

One of the better-understood forms of cell death, apoptosis still manages to mystify scientists. "Sometimes our cells die when we really don't want them to — say, in neurodegenerative diseases. And sometimes our cells don't die when we really do want them to — say, in cancer," Ferrell said. "And if we want to intervene, we need to understand how apoptosis is regulated."

The study was published in *Science* Aug. 10. Ferrell is the senior author. Postdoctoral scholar Xianrui Cheng, PhD, is the lead author.

Spreads like wildfire

Trigger waves require two main elements: a positive feedback loop and a threshold — think falling dominoes. One domino collapses on another and triggers that domino to topple onto the next. The threshold is the force necessary to completely knock the tile over; a domino just shy of its threshold would teeter and rock back into a vertical position, whereas one that's reached the threshold would fall. Trigger waves in an apoptotic cell are governed by that same phenomenon. Once cell death is initiated, by way of disease or something else, specific killer proteins in the cell, called caspases, activate. These proteins then float to other caspases and activate them; those follow suit until the entire cell has to pack it in.

"It spreads in this fashion and never slows down, never peters out," Ferrell said. "It doesn't get any lower in amplitude because every step of the way it's generating its own impetus by converting more inactive molecules to active molecules, until apoptosis has spread to every nook and cranny of the cell."

To see how death takes over a single cell, Cheng and Ferrell used Xenopus frog eggs. One egg is a single cell, and as cells go, these are enor-

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Common skin cancer can signal increased risk of other cancers

By Krista Conger

People who develop abnormally frequent cases of a skin cancer known as basal cell carcinoma appear to be at significantly increased risk for developing other cancers, including blood, breast, colon and prostate cancers, according to a preliminary study by researchers at the School of Medicine.

The increased susceptibility is likely caused by mutations in a panel of proteins responsible for repairing DNA damage, the researchers found.

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Basal cell carcinomas are common. More than 3 million cases a year are diagnosed nationwide.

"We discovered that people who develop six or more basal cell carcinomas during a 10-year period are about three times more likely than the general population to develop other, unrelated cancers," said Kavita Sarin, MD, PhD, assistant professor of dermatology. "We're hopeful that this finding could be a way to identify people at an increased risk for a life-threatening malignancy before those cancers develop."

Sarin is the senior author of the study, which was published online Aug. 9 in *JCI Insight*. Medical student Hyunje Cho is the lead author.

Largest organ

The skin is the largest organ of the body and the most vulnerable to DNA damage caused by the sun's ultraviolet rays. Try as one might, it's just not possible to completely

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Scientists tie specific brain circuit to sociability in mice

By Bruce Goldman

STEVE FISCH

Robert Malenka said drugs activating a particular subtype of serotonin receptors found in a region of the brain could prove therapeutic in ameliorating the social deficits caused by autism.

Social behavior in mouse models of autism spectrum disorder normalized when investigators triggered the release of a specific signaling substance, serotonin, in a single part of the animals' brains, according to a study from the School of Medicine.

"This points to a previously understudied brain mechanism that contributes to an inability to derive pleasure from social interactions," said Robert Malenka, MD, PhD, professor and associate chair of psychiatry and behavioral sciences.

The brain mechanisms underlying sociability and social deficits are poorly understood, complicating attempts to find effective treatments for autism spectrum disorders, schizophrenia and other neuropsychiatric disorders marked at least in part by social withdrawal. In the study, experimental manipulations triggered extensive release of serotonin in a region of the mice's brains called the nucleus accumbens. Malenka said drugs activating a particular subtype of serotonin receptors found in this

See AUTISM, page 6

Hidden DNA sequences tied to schizophrenia, bipolar risk

By Krista Conger

A series of repeated DNA sequences unique to humans may be linked to the development of schizophrenia and bipolar disorder, according to a new study by researchers at the School of Medicine.

The finding suggests that the rapid evolutionary changes that led to the extraordinary complexity of the human brain may have predisposed our species to psychiatric diseases not found in other animals. It also outlines a possible way to one day identify people at risk for, and ways to intervene in, these disorders.

Although the sequences exist within a small stretch of DNA that has been previously linked to schizophrenia and bipolar disorder, they represent a kind of genomic stutter that is particularly difficult to detect using conventional sequencing methods. As a result, they've been effectively hidden from researchers attempting to pinpoint a specific mutation that contributes to risk for the diseases.

"The human genome reference sequence shows only 10 repeats of this 30-nucleotide sequence, but we've found that individuals actually have from 100 to 1,000 repeats, and that the sequence itself can vary," said professor of developmental biology David Kingsley, PhD. "In contrast chimpanzees and other primates have just one repeat of the sequence, indicating that the region has greatly expanded during human evolution. Some of the sequence variants now found in people are also closely associated with the development of schizophrenia and bipolar disorder."

Kingsley, who is a Howard Hughes Medical Institute investigator, is the senior author of the research, which was published Aug. 9 in the *Journal of Human Genetics*. Graduate student Janet Song and former postdoctoral scholar Craig Lowe, PhD, share lead authorship of the study.

The evolution of our brains

Song and Lowe didn't start out intending to study psychiatric disorders. Instead, Kingsley and his colleagues have long been interested in identifying regions of the human genome that differ from those of our closest animal relatives such as primates. Studying these regions is a way to trace evolutionary changes that confer some of our uniquely human traits.

But many of these seeming advances, such as walking upright or changing jaws and teeth to accommodate different foods or larger brains come at a cost. New styles of walking and new diets in humans have brought with them a high incidence of bad backs, sore knees and impacted wisdom teeth. Some researchers have wondered whether the rapid evolution of our large, complex brains could also be the reason why humans suffer some psychiatric disorders that don't appear to afflict members of other species.

David Kingsley

"Human evolution has given us big and active brains and a remarkable cognitive capacity," Kingsley said. "But a side effect of this could be an increased risk for other, less desirable outcomes."

About 3 percent of people worldwide suffer from bipolar disease or schizophrenia, which have few effective treatments. Sufferers are at increased risk of suicide, and the disorders are one of the top causes of disability. Although the two diseases are distinct, many previous efforts to identify their genetic causes have implicated genes involved in the transport of calcium into and out of brain cells in response to external signals. These calcium channels are responsible for many critical biological processes, and drugs modulating their function are widely used to treat high blood pressure and cancer.

One calcium channel gene in particular, CACNA1C, has repeatedly been associated with a risk of both schizophrenia and bipolar disorder. But until now, no one has been able to pinpoint any specific disease-associated DNA mutations within the coding region of CACNA1C. Instead, the culprit seemed to lurk within a stretch of 100,000 nucleotides in a noncoding portion of the gene called an intron.

> Complex brains could be a reason why humans suffer mental disorders that don't appear to afflict other species.

In their quest to identify how the genome sequences of humans and primates vary, Song and Lowe discovered that the human CACNA1C gene contains a sequence that repeats as many as 1,000 times a 30-nucleotide sequence that is found only once in the chimpanzee genome. Large, repeated arrays such as these often form structures that can affect the expression of nearby genes but, because they are unstable when grown in many bacterial strains in the laboratory, they can stymie traditional sequencing methods.

'Invisible to researchers'

"This massive array was, for the most part, invisible to researchers," Kingsley said. "It caught our attention because it is located in the region that had been previously linked to schizophrenia and bipolar disease risk. We wondered whether, given all the 'flavors' of variation in length and sequences, some combinations of the repeats might confer increased risk to psychiatric disorders by affecting the expression levels of the CACNA1C gene."

The researchers investigated whether certain sequence combinations in the repeated array correlated with a diagnosis of schizophrenia or bipolar disorder in participants in the 1,000 Genomes Project — an international effort to catalog and understand human genetic variation. They found that although some combinations were strongly linked to the development of schizophrenia or bipolar disorder, others were enriched in patients with protective versions of the gene. When Kingsley and his colleague tested different versions of the arrays for their effects on gene expression in cultured human neural precursor cells, the risk- and protective-associated sequence arrays showed variable abilities to modulate gene expression.

"There's been a long-standing area of speculation in the literature that this kind of repeated array is likely to both change gene function and generate new variants that will further alter expression levels," Kingsley said. "It's a great way for evolution to experiment by 'tuning' genes to achieve variable outcomes."

The researchers' experiments suggest that those array combinations that appear to protect against the development of schizophrenia and bipolar disorder could increase the expression of CACNA1C. However, different cells and brain regions may react differently to the sequences, and it's not yet clear precisely how changes in CACNA1C expression affect disease risk. Regardless, the involvement of a calcium channel gene is of interest because drugs targeting these channels are already widely used in humans.

"Better classification of patients based on their repeat arrays in the CACNA1C gene may help identify the particular patient cohorts most likely to respond to existing calcium channel drugs," Kingsley said. "The best match between patients and drugs is not known right now, but we do hope that genotype-based drug targeting may lead to improved treatments in the future for these devastating diseases."

The research was supported by the National Institutes of Health, the National Science Foundation and the Howard Hughes Medical Institute.

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

$10 million pledge will support next generation of biomedical innovators

By Eileen DiFranco

The Blavatnik Family Foundation has pledged $10 million to Stanford Medicine for the training of graduate students in the biomedical sciences, powering the innovation and independence of talented young researchers.

The Blavatnik Family Fellowship Fund at the School of Medicine will support PhD fellowships that allow young scientists enrolled in the Stanford Biosciences to pursue investigative directions that inspire their creativity and passion.

The fund will support five Blavatnik Fellows a year in perpetuity and builds upon a previous $2 million Blavatnik Family Foundation commitment to assist Stanford bioscience graduate students in their research.

"Len Blavatnik's vision and generosity — and the impact it will have on the future of biomedical research — are impossible to overstate," said Lloyd Minor, MD, dean of the School of Medicine. "His contribution will directly benefit our graduate students and empower them to pursue their passions. It is a legacy that will ultimately lead to new discoveries in the field and improved care for patients around the world."

Len Blavatnik, head of the Blavatnik Family Foundation, said, "We are proud to support the biomedical research being conducted at Stanford School of Medicine, one of the world's most elite biomedical sciences institutions. We look forward to celebrating many ground-breaking discoveries in the years ahead."

> The funding will support five graduate students a year in perpetuity.

In the conventional funding model for bioscience graduate education, students often must join the laboratories that have funding — not necessarily labs that are pursuing research that speaks to their own investigative interests. To combat the dampening effect this has on the innovation and independence of talented young scientists, Stanford Medicine, through its Biomedical Innovation Initiative, guarantees a full four years of funding to every incoming biomedical graduate student.

This commitment has yielded demonstrable benefits at Stanford Medicine. The number of incoming students who accept admission has risen from around 50 percent to the mid-60s range, and the initiative also has aided the School of Medicine's goal of diversifying the student body. The Blavatnik Family Fellowship Fund will build on these successes and, as the first endowment funds raised for the program, secure financial support for five fellowships permanently.

The Blavatnik Family Foundation is an active supporter of leading and transformative educational, scientific, cultural and charitable institutions worldwide. Among the foundation's programs are the Blavatnik Awards for Young Scientists that support early career scientists and engineers in the U.S., U.K. and Israel.

To date, the foundation has contributed hundreds of millions of dollars to more than 250 institutions worldwide. The foundation was established by Len Blavatnik, a global industrialist and philanthropist. He is the founder and chairman of Access Industries. **ISM**

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STANFORD MEDICINE

5 QUESTIONS

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

Donna Zulman on engaging high-need patients

Once patients leave the doctor's office, their health outcomes largely depend on continued engagement in their own care, including appointment follow-up, treatment completion and self-care practices at home. This can be challenging, particularly for "high-need" patients — that is, patients who face socioeconomic challenges, have multiple chronic illnesses or otherwise grapple with other external factors that impede their access to health care.

Donna Zulman, MD, assistant professor of medicine at Stanford, hopes to transform care for these high-need patients by finding effective strategies that boost engagement in their own care. Achieving this goal may require specialized programs that provide extra time, resources and autonomy to patients, she said. Zulman also suggests individually tailored approaches may be critical to build trust and lasting relationships with high-need patients.

The effort hinges on a strong core of health care professionals who not only forge personal connections with patients, but who also help patients find ways to overcome barriers to improving their health. One provider, for instance, found that a patient with heart failure didn't have a car and likewise couldn't take the bus or walk due to his condition, so the provider helped him obtain taxi vouchers.

Zulman and her colleagues worked with leaders and clinicians at 12 different intensive outpatient programs in Northern California, collecting information about the most common barriers to high-need patient engagement and the measures the leaders and clinicians devised to boost patient participation. A paper detailing the researchers' work was published online Aug. 10 in the Journal of General Internal Medicine.

In a recent interview, science writer Hanae Armitage talked with Zulman about the paper's findings.

1 What are some of the characteristics of a high-need patient?

ZULMAN: The term "high-need" refers to a group of patients who typically have complex medical, social or behavioral challenges and account for disproportionate health care spending — sometimes described as the 5 percent of patients who account for 50 percent of health care spending in this country. This population includes patients with advanced illnesses or disabilities, older adults with frailty and patients with multiple chronic conditions.

2 What are the key barriers that prevent high-need patients from completing intensive outpatient programs?

ZULMAN: When we asked intensive outpatient program leaders and clinicians about barriers that impede patient engagement, the most common structural issue was care fragmentation across health systems. Many high-need patients receive care from multiple physicians, clinics and social services in different settings.

At an individual level, challenges like financial insecurity, mental illness and substance use, physical symptoms and limitations, and a lack of social support were extremely common. One thing that stood out was the prevalence of socio-behavioral factors that pose major challenges for patients, including distrust of the health care system, transportation challenges, housing instability and other issues relating to the neighborhood and social environment.

3 How should health care professionals rethink their approach to outpatient programs to boost participation?

ZULMAN: Most of the people we interviewed for our study described patient-engagement approaches in three general domains. First, they described strategies that facilitate patient communication and participation in recommended health-related activities. These often involved concrete resources, such as arranging for copay reductions or transportation vouchers, assisting with housing applications to help a patient identify a safer living situation and co-attending appointments to help coordinate care from different doctors. These strategies serve as communication lines and access bridges, helping patients overcome the physical barriers that impede the use of available services and resources.

Donna Zulman

A second set of strategies focused on building relationships and trust. Often, the programs begin by attempting to meet patients' basic or most pressing needs, a process that may involve addressing housing instability, food insecurity, transportation challenges, employment status or social isolation before tackling health issues. Some patients have had negative experiences with the health care system, and building trust is central to longer-term engagement.

Finally, a third set of strategies focused on helping patients gain insight, set goals and problem-solve. Program representatives frequently described a process in which they initially problem-solved for patients, particularly when patients faced critical needs around housing, food insecurity and finances. Over time, they gradually introduce patients to skills and coping mechanisms so that they could begin to problem-solve for themselves. Through these methods, programs can help patients gain the skills needed to monitor and address their health issues, develop coping mechanisms and seek the care they need.

4 How can health systems design intensive outpatient programs that succeed in engaging high-need patients?

ZULMAN: We identified a number of program features that appear to facilitate high-need patient engagement and could inform the design of future programs. First, most teams included staff from diverse disciplines — such as a physician, nurse, social worker and psychologist — which increased the likelihood that someone on the team had the necessary expertise to address the patient's needs. Including team members who had a shared experience with patients, whether that referred to roots in the same city, language concordance or a history of homelessness, was also described as helpful. Many programs also sought staff who are proactive, creative and flexible, all of which are a boon to engaging high-need patients, as it often involves unconventional activities that deviate from standard practice.

We heard all sorts of interesting stories about program staff who found time to visit patients in their homes, take them fishing, stand with them in line at the DMV and even go out in search of a prosthetic leg. These time-intensive and intimate activities were seen as pivotal moments that led to trusting relationships. So programs require adequate time and resources to build relationships with patients, and they need to have the autonomy to address patients' needs on their own terms.

5 How do you scale these new models to a larger population?

ZULMAN: That will require substantial effort and creativity because the heart and soul of these programs is the passion and dedication of the core staff, and that's not something that can be easily scaled. However, some programs are experimenting with creative approaches that employ health coaches, medics and members of the community to assist with patient-engagement efforts. There are now a number of multisite collaborative efforts to share effective practices and help train new teams. Program leaders and researchers are working hard to understand the key ingredients of successful programs, and to develop tools and resources that will help disseminate the most promising approaches. **ISM**

■ OBITUARY

Anesthesiologist and beloved teacher Kevin Malott dies at 49

By Erin Digitale

Kevin Malott, MD, a clinical associate professor of anesthesiology, perioperative and pain medicine at the School of Medicine, died July 26 in San Mateo, California, after a brief illness. He was 49.

Kevin Malott

Malott is remembered at Stanford as a beloved teacher, expert physician and compassionate colleague. He excelled at helping trainee anesthesiologists learn new skills, was sought out for second opinions on difficult cases, and was known for using his humility, kindness and empathy to defuse stressful situations in the operating room.

"He was a very gentle person who always saw the good in people and was extremely committed to his patients," said Ronald Pearl, MD, professor and chair of the Department of Anesthesiology, Perioperative and Pain Medicine.

Malott first came to Stanford as an anesthesiology resident in 1996. He joined the faculty at Stanford in 2001, and since 2015 specialized in treating pediatric patients at Lucile Packard Children's Hospital Stanford.

"He was one of the most calm and generous souls we had in our department, always willing to step up and help other people," said Anita Honkanen, MD, clinical professor of anesthesiology, perioperative and pain medicine and the service chief of anesthesia at Packard Children's. "I was so happy when he came to pediatric anesthesia full-time. He really liked being able to care for our pediatric patients."

Malott was born Dec. 26, 1968, and grew up in the Tehachapi and Santa Barbara areas of California. He completed his undergraduate studies at the University of California-Irvine in 1991, receiving bachelor degrees in biology and in psychology. He earned his medical degree from the Dartmouth Geisel School of Medicine in 1995.

Malott liked the challenge of his complex cases at Stanford, according to his wife, Jocelyn Malott, a nurse practitioner in orthopedic oncology at Stanford Health Care. "He was very good with children and with parents who were nervous, keeping them at ease," Jocelyn Malott said. Since her husband's death, she has received many emails from anesthesiologists he trained, sharing how he was able to help them learn during challenging surgeries. "On hard cases, he could step in without putting people down," she said. "Even in the most urgent situations, he could still provide a teaching moment without judgment."

In 2014, the graduating anesthesiology residents voted to give Malott the H. Barrie Fairley Excellence in Teaching Award, an annual award honoring the residents' favorite instructor.

Global medical missions

In his free time, Malott enjoyed hiking, travel, reading, playing the piano and attending San Francisco Giants games. Between 1999 and 2016, he participated in medical missions to several developing countries to assist organizations that provide plastic surgery services for children, such as repairing cleft lips and palates, and assisting burn victims.

Malott also had a well-known love of skateboarding and got some of his anesthesiologist colleagues to join him in his favorite ritual for settling his mind before shifts in the operating rooms: Arriving at Stanford early in the morning, he liked to park at the top of one of the parking structures and skateboard down through the expanses of empty ramps on his way to work.

Malott was predeceased by his father, Steven Malott. In addition to his wife, he is survived by his mother and stepfather, Sandy and Larry Short, of Tehachapi; daughter Elissa Malott of San Jose; son Justin Malott of San Jose; stepsons Paul Barrera and Jason Barrera, both of San Francisco; brother and sister-in-law Mark and Linda Malott, of Lancaster, California; stepbrother and stepsister-in-law Darren and Tammy Short, of Tehachapi; and five nieces.

A memorial service will be held at Stanford Memorial Church on Aug. 23 at 4 p.m.

Memorial donations may be made to the Kevin Malott Memorial Fund, which has been founded by his wife in the School of Medicine's Department of Anesthesiology, Perioperative and Pain Medicine to establish an award for graduating anesthesia residents. Contributions can be made via the "Make a Gift" link at http://med.stanford.edu/anesthesia.html. The family would also appreciate memorial donations to Medical Missions for Children, at http://www.mmfc.org/, or to Malott's church, St. James the Apostle Catholic Church, 34700 Fremont Blvd., Fremont, CA, 94555. **ISM**

Bacterial armor could be new target for antibiotics

By Tom Abate

For over a century, scientists have studied E. coli, one of the bacteria that cause food poisoning, as a model for fighting infections. Such research has led to a variety of antibiotics that penetrate the protective cell walls of bacteria to kill them.

Now, a multi-university study overseen by KC Huang, PhD, associate professor of bioengineering and of microbiology and immunology, reveals that E. coli has managed to keep a big secret about its defenses.

He and his collaborators report in a paper published July 18 in *Nature* that scientists had overlooked the astonishing physical strength of the thin outer membrane that clings to E. coli's stout cell wall. Huang is the senior author of the study. The lead author is former postdoctoral scholar Enrique Rojas, PhD.

Scientists have long known that many bacteria have an outer membrane. But until now, they thought of it as a layer of shrink wrap that simply made it tougher to get antibiotics into cells. But as the new study shows, the outer membrane physically protects the cell and could be a good target for a new class of antibacterial drugs.

"We've discovered that the outer membrane can act as a suit of armor that is actually stronger than the cell wall," Huang said. "It's humbling to think that this function had been hiding in plain sight for all these years."

Huang said the findings suggest new infection-fighting strategies for the roughly half of all bacterial species that, like E. coli, have outer membranes. "If we can attack the outer membrane, infectious bacteria will be pre-weakened for targeting with antibiotic treatments that disrupt cells in other ways," he said.

Chemical shields

All bacteria have a cell wall that surrounds and protects the cell's inner workings. Many decades ago, scientists discovered that E. coli and many other bacteria have an additional layer, called an outer membrane, that surrounds their cell walls.

Since its discovery, this outer membrane has been used as a way to classify bacteria into those that do and do not react to a common staining technique, called a Gram stain. Bacteria with outer membranes do not react to the chemical stain are called Gram-negative. Bacteria with naked cell walls react to the stain and are classified as Gram-positive.

Both kinds of bacteria can become infectious and, when this occurs, the presence or absence of an outer membrane can also help determine how responsive they will be to antibiotics. Gram-negative bacteria tend to be more resistant to antibiotics.

"Scientists knew that outer membranes were chemical shields," Huang said. "Thus, it was easy to relegate this third layer to an annoyance when dosing the cell with antibiotics."

Surprising strength

In recent years, however, researchers have picked up clues that the outer membrane is more important than they'd thought. In one study, Huang's lab removed the cell wall of E. coli but left its outer membrane intact. Unsurprisingly, the bacteria lost their cucumber shape and became blobs. But a large fraction of these blobs survived, multiplied and ultimately reproduced new cucumber-shaped E. coli.

Rojas said that study was a clue that the outer membrane must play important structural and protective roles. "We just listened to the data. Science is about data, not dogma," said Rojas, now an assistant professor of biology at New York University.

Over the last four years, working with collaborators from UC-San Francisco and the University of Wisconsin-Madison, the researchers tested the outer membrane's structural powers.

They suddenly collapsed the pressure inside the bacteria, but instead of causing the cell wall to massively shrink, as prevailing assumptions would have predicted, they found that the outer membrane was strong enough to almost entirely maintain E. coli's cucumber shape.

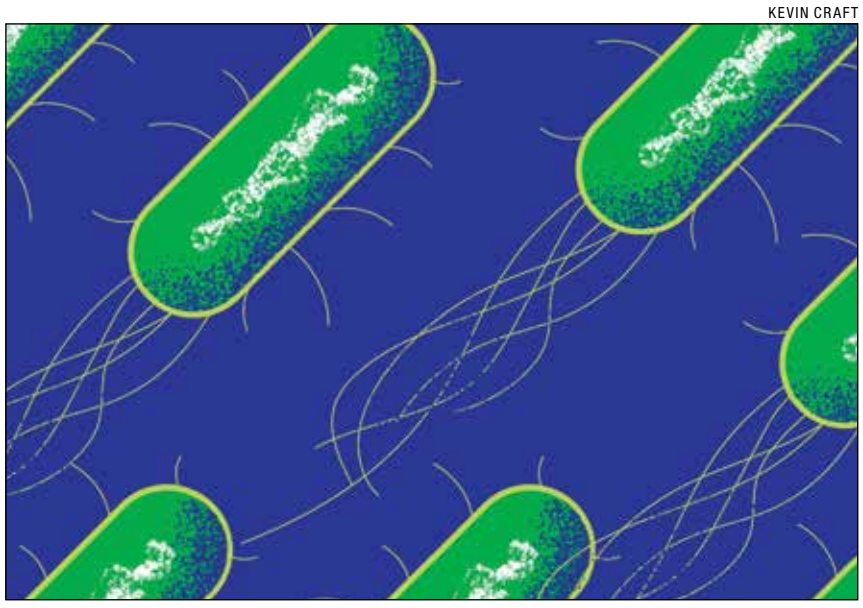
In other experiments, they put E. coli cells through two hours of rapid increases and decreases in pressure. E. coli cells normally shrug off these repeated insults and grow as if no changes at all had occurred. However, when the researchers weakened the outer membrane, cells died quickly.

"The presence or absence of a strong outer membrane is the difference between life and death," Huang said.

The experiments identified a handful of components that give the outer membrane its surprising strength. Drugs that destabilize the deceptively thin outer layer could help destroy infectious bacteria, Huang said.

Huang added that the findings are part of an emerging field of study called mechanobiology. Whereas scientists once viewed cells as sacks of chemicals to be studied by chemical means, today a confluence of tools reveal the infinitely complex structural properties that make cells and organs tick.

KEVIN CRAFT



"It's a very exciting time to be studying biology," Huang said. "We are approaching the point at which our tools and techniques are becoming precise enough to discern, sometimes at almost the atomic level, the physical rules that give rise to life."

Huang is also a member of Stanford Bio-X and a faculty fellow at Stanford ChEM-H. Other Stanford co-authors are Julie Theriot, PhD, professor of biochemistry and of microbiology and immunology, and a member of Stanford Bio-X; graduate student Amanda Miguel; postdoctoral scholar Pascal Odermatt, PhD; and undergraduate student Lillian Zhu.

This work was funded by the National Institutes of Health, the National Science Foundation, the Stanford Systems Biology Center and Simbios Center for Physics-Based Computation at Stanford, the Howard Hughes Medical Institute, the Swiss National Science Foundation, and the Allen Discovery Center program through the Paul G. Allen Frontiers Group.

Stanford's departments of Biomedical Engineering and of Microbiology and Immunology also supported the work. The Department of Bioengineering is jointly operated by the School of Medicine and the School of Engineering. ISM

After many years, source of patient's headaches identified

By Patrick Bartosch

Rachel Hale knew her adolescence was unusual. The headaches, the nausea, the dehydration, the blood draws leaving scars on her arm — this wasn't what most other kids her age were going through.

By the time she was 24, Hale was on her fourth diagnosis and had been on headache medication for years. Her condition prevented her from participating in sports and social events. Sometimes she couldn't even go out to eat with friends. She had bounced from physician to physician and hospital to hospital, without much relief.

STEVE FISCH

Rachel Hale spent years suffering from headaches and nausea before a specialist at Stanford Health Care diagnosed the cause.

Then, in November 2017, when Hale was at Stanford Hospital because she was having trouble getting out of bed, she met Linda Nguyen, MD. A clinical associate professor of gastroenterology and hepatology at the Stanford School of Medicine, Nguyen was assessing Hale's gastrointestinal issues.

Nguyen had recently heard from Ian Carroll, MD, a headache and orofacial pain specialist at Stanford. Carroll had shared information with her about cerebrospinal fluid leaks: He said the leaks were characterized by chronic, intractable nausea in addition to ringing in the ears, vomiting and headaches.

When Nguyen contacted Carroll about Hale, he immediately took an interest in her case. He ran scans and diagnosed a CSF leak. "I don't think I'll ever forget doing the first diagnostic test where he just had me lie flat," recalled Hale. "It was the first time my headache has ever gone away, and it was a huge 'Aha!' moment for me."

A CSF leak occurs when the meninges — a covering that protects the brain and spinal cord and holds the cerebral fluid in place — forms a tear, allowing the fluid to escape. CSF leaks can occur spontaneously, but people with Marfan and Ehlers-Danlos syndromes, both connective tissue disorders, are at the highest risk.

A patch made from blood

To treat the CSF leak, Carroll performed an epidural blood patch. In the procedure, the patient's own blood is injected into the meninges, creating a seal over the part where the bag is torn.

After her first blood patch, Hale improved substantially, and Carroll was confident they were on the right path. "We want multiple dimensions across her life to improve so she can return to function and do the things a young woman wants to do with her life instead of seeing doctors all the time," said Carroll, who is also an assistant professor of anesthesiology, perioperative and pain medicine at the School of Medicine.

Carroll believes that CSF leaks may be more common than anyone thought, and often misdiagnosed. He speaks from personal experience: His daughter had a CSF leak that had gone undiagnosed. That's when he began to think about the interplay of different syndromes and symptoms, and how important it is for a major academic medical center like Stanford Health Care to collaborate across departments.

Orthostatic headache, or headache that is worse when upright, is a key feature of a CSF leak, but is also a common feature in patients with postural orthostatic tachycardia syndrome, or POTS.

"Patients shouldn't have to wander from doctor to doctor until they randomly interact with one who happens to know that some people are at greater risk of developing a leak," Carroll said. "After the personal experience I had with my daughter, I started reaching out to the Stanford Headache Clinic as well as the POTS and Marfan clinics. Now we're all reading about these leaks, and it has created a great dialogue."

Hale laughed when Carroll insisted she watch three videos and read a paper about her procedure before he would even talk to her. But in the end, his advice was right: "He involved me a lot and kept me updated, which I really, really appreciated," she said.

Hale's headaches aren't as common as they once were, and the sensory overload feelings are subsiding. She will continue to receive the blood patch procedures to keep her symptoms under control.

"This blood-patching thing, from a nerdy, scientific perspective, I think is so fascinating," she said. "I love it." ISM

New algorithm could improve diagnosis of rare diseases

By Erin Digitale

Today, diagnosing rare genetic diseases requires a slow process of educated guesswork. Gill Bejerano, PhD, associate professor of developmental biology and of computer science at Stanford, is working to speed it up.

In a paper published July 12 in *Genetics in Medicine*, Bejerano and his colleagues describe an algorithm they've developed that automates the most labor-intensive part of genetic diagnosis: that of matching a patient's genetic sequence and symptoms to a disease described in the scientific literature. Without computer help, this match-up process takes 20-40 hours per patient: The expert looks at a list of around 100 of the patient's suspicious-looking mutations, makes an educated guess about which one might cause disease, checks the scientific literature, then moves on to the next one.

The algorithm developed by Bejerano's team cuts the time needed by 90 percent.

"Clinicians' time is expensive; computer time is cheap," said Bejerano, who worked with experts in computer science and pediatrics to develop the new technique. "If I'm a busy clinician, before I even open a patient's case, the computer needs to have done all it can to make my life easier."

A Phrank approach

The algorithm's name, Phrank — a mashup of "phenotype" and "rank" — hints at how it works: Phrank compares a patient's symptoms and gene data to a knowledge base of medical literature, generating a ranked list of which rare genetic diseases are most likely to be responsible for the symptoms. The clinician has a logical starting point for making a diagnosis, which can be confirmed with one to four hours of effort per case instead of 20-40 hours.

"Clinicians' time is expensive; computer time is cheap."

The mathematical workings of Phrank aren't tied to a specific database, a first for this type of algorithm. This makes it much more flexible to use.

Phrank also dramatically outperforms earlier algorithms that have tried to do the same thing, according to the paper. Bejerano's team validated Phrank on medical and genetic data from 169 patients, an important advance over earlier studies in the field. Prior studies had tested algorithms on made-up patients instead because real-patient data for this research is hard to come by.

Gill Bejerano

"The problem is that this test [using synthetic patients] is just too easy," Bejerano said. "Real patients don't look exactly like a textbook description." On data from real patients, one older algorithm ranked the patient's true diagnosis 33rd, on average, on the list of potential diagnoses it generated; Phrank, on average, ranked the true diagnosis fourth.

Phrank also holds potential for helping doctors identify new genetic diseases, Bejerano said. For example, if a patient's symptoms can't be matched to any known human diseases, the algorithm could check for clues in a broader knowledge base. "You might get the result that mouse experiments cause phenotypes similar to your patient, that you may have found the first human patient that suffers from this disease," Bejerano said.

Ultimately, "nobody is going to replace a clinician making a diagnosis," he said. But new technology could help experts use their time more efficiently, helping many more patients get diagnosed, he said.The lead authors of the paper are graduate students Karthik Jagadeesh, MS, and Johannes Birgmeier, MS.

Other Stanford co-authors are Jon Bernstein, MD, PhD, associate professor of pediatrics; undergraduate student Cole Deisseroth; and former graduate students Harendra Guturu, PhD, and Aaron Wenger, PhD.

The work was funded by Stanford graduate fellowships, Stanford Bio-X, DARPA, the David and Lucile Packard Foundation and Microsoft.

Stanford's departments of Developmental Biology, of Computer Science and of Pediatrics also supported the work. **ISM**

ARTEMTATION / PIXABAY

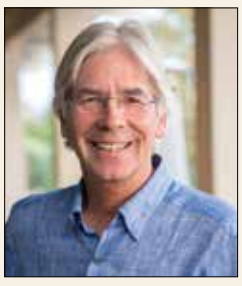
Christopher Gardner busts myths about milk

By Jennifer Huber

Milk used to be simple. Your local dairy, say Berkeley Farms, delivered it to your doorstep.

Today, we are faced with an unfathomable array: nonfat, lowfat or whole milk? Almond, soy, rice, hemp or oat milk? From goats or cows? With or without the lactase enzyme? Raw or pasteurized? Plain or flavored? There's even an ongoing controversy over which of these drinks can be called milk.

Stanford nutrition scientist Christopher Gardner, PhD, wants to help consumers cut through the confusion. In an interview, he discussed some of the biggest misconceptions about the beverage.



Christopher Gardner

Most of us grew up believing that milk is important for children to build strong bones and for the elderly to prevent osteoporosis. But milk, a good source of calcium, isn't necessarily the most critical factor for bone health, said Gardner, the Rehnborg Farquhar Professor and a professor of medicine.

"There are countries like Japan and India where the population is predominantly lactose intolerant, where milk intake is low and hip fracture rates are also low. But many of those cultures do more weight-bearing activities than Americans," he said. "It's better to be physically active than drink milk as a way to strengthen your bones."

Studies have shown that drinking milk can improve your bone density, but whether it helps prevent bone fractures is debatable, he added.

Do we need cow's milk?

But don't young kids need milk? According to Gardner, it depends on what kind of milk. Breast milk is incredibly important, but cow's milk isn't, he said.

"This myth goes way back to before the food pyramid when the National Dairy Council offered to provide nutrition material to schools for free. And in all those materials, they said that you need multiple servings of dairy every day for a healthy diet," Gardner said. "That was never agreed on. A lot of people are lactose intolerant, and you don't need it."

Milk can be healthier than other options, like soda. He recommended checking the nutrition panel to make sure the milk isn't just as sugary as soda though, particularly with plant-based milks. "The popular vanilla and chocolate versions of the plant-based milks are often loaded with added sugar. Even the plain is typically sweetened, but you can get unsweetened," he said. "The lactose in milk isn't that bad, so there is no need to water it down. Just avoid milks with added sugars."

The nutrition label also allows you to compare the amount of fats, protein, carbohydrates and vitamins in each type of milk. "For example, the plant-based milks generally don't have saturated fat like cow's milk, so they don't raise LDL-cholesterol as much as dairy milk, but they do have about the same amount of calcium," he said. "And soy milk has the same amount of protein as dairy milk, but almond milk has much less protein."

Another common misunderstanding is that 2-percent milk means that 2 percent of the calories are from fat. Really, it means that 2 percent of the weight is from fat. In 2-percent milk, 35 percent of the calories are from fat, Gardner noted. "Whole milk has close to 50 percent of its calories as fat, and 1-percent milk has about 20 percent," he said.

Does milk help with weight loss?

However, your milk's fat content may not affect your weight. The old belief was that drinking whole milk will make you fat and skim milk will help you lose weight. But this was refuted by Harvard's Nurses' Health Study, which followed the diets of over 100,000 nurses for more than 30 years, including how their diets changed.

"It's better to be physically active than drink milk as a way to strengthen your bones."

"The Harvard study found that switching back and forth from whole fat to 2 percent to 1 percent was not associated with changes in weight," Gardner said.

But does drinking more milk help with weight loss? Some small, short-term studies showed that people lost weight if they drank more milk. According to Gardner, this raises the always-present nutrition-research challenge: Was it drinking more milk or was it consuming less of something else that caused the weight loss?

And what about raw milk? Raw milk proponents argue that pasteurization kills off important healthy bacteria, but Gardner said that it's difficult to prove any health benefits from these bacteria. Some raw milk producers also claim it is easier to digest. However, a study overseen by Gardner found that lactose intolerant participants had the same symptoms with raw and pasteurized milk.

And what does Gardner himself drink? He said he gave up cow's milk for ethical reasons.

"Now, I drink unsweetened soy milk," he said. "In our household, my wife doesn't digest dairy milk very well, so we don't even have it around. My four boys all drink unsweetened soy milk." **ISM**

Revealed: The molecular mechanism underlying hypertrophic cardiomyopathy

By Bruce Goldman

About 1 in every 500 people is born with hypertrophic cardiomyopathy, a genetic disease caused by any one of numerous mutations that, mysteriously, cause heart muscle to contract with too much force.

You'd think that hypertrophic cardiomyopathy would make you a natural athlete. Instead, it can be lethal. "If you're carrying one of these mutations, it's as if you're out for a jog. The problem is, you're doing that 24 hours a day for your whole life," said Jim Spudich, PhD, professor of biochemistry at the School of Medicine. At some point, your heart begins to feel the effects, becoming swollen, then fibrotic, and eventually giving out.

Now, researchers have discovered the mechanism behind this workaholic heart. The findings were reported in a paper published online Aug. 13 in the Proceedings of the National Academy of Sciences. Spudich is the senior author. Lead authorship is shared by Stanford postdoctoral scholars Darshan Trivedi, PhD, and Saswata Sarkar, PhD; and by Robert Anderson, a researcher at MyoKardia, a company co-founded by Spudich.

Spudich has spent decades studying, at the molecular level, how muscles contract — and, in particular, the workings of myosin, a key constituent of every muscle cell, including the ones composing heart muscle.

Myosin is a protein and a hard-working little motor of sorts, whose dynamic action contributes to the overall contraction of a muscle. But it only works part-time, spending much of its existence in a posture akin to that of a sleeping flamingo, with its head tucked tightly into its torso. That's just as it should be, from the standpoint of optimal heart function.

Like all proteins, myosin molecules are made up of amino acids. There are 20 different types of amino acids, each with its own biochemical quirks and distinctive shape. Spudich and his colleagues discovered that many mutations associated with hypertrophic cardiomyopathy, although they occur at different points along the myosin gene's sequence, often wind up affecting amino acids on the same surface of the folded protein's outer edge, altering the myosin molecule in ways that coax it out of its sleeping flamingo posture.

The changed postural preference, in turn, keeps the myosin molecule from spending enough time snoozing on the job, collectively causing constant overdrive in the heart muscle's power output.

The study was supported by the National Institutes of Health, the Stanford Child Health Research Institute and the American Heart Association. ISM

Cells

continued from page 1

mous, making them a prime candidate to observe how death spreads from one end of the cell to the other, which can be done with the naked eye.

To start, the two scientists took fluid from the egg and inserted it into Teflon tubes, which were several millimeters long, and initiated apoptosis through a molecular "death signal." By using a fluorescent technique linked to the activation of apoptosis, Ferrell and Cheng could watch as the bright green glow moved its way down the tube at a constant speed, indicating that apoptosis was spreading via trigger waves, as opposed to some other more rudimentary mechanism, such as diffusion, which slows down as it moves.

The question was, did apoptosis also spread like that in cells as they naturally occur?

Turning to fluorescence microscopy here proved more difficult, as intact frog eggs are quite opaque. However, Cheng and Ferrell noticed that when frog eggs die, a sort of ripple of pigmentation occurs at the egg's surface. The scientists saw that during death, a dark ripple moved like a curved line across the egg at a constant speed from one side to the other. The speed of this surface wave, which was constant and did not slow down, tipped them off to trigger waves here too. So to further confirm, they analyzed individual dying eggs: Every egg that had undergone this surface wave contained activated caspase, whereas the eggs that had not yet undergone the waves did not — more evidence that trigger waves propagate cell death in an intact cell too.

Investigating other trigger waves

So far, apoptosis is the only form of cell death in which trigger waves have been identified, but Ferrell is investigating other processes in biology to see if the continual waves might play a role.

Now, they're looking into whether trigger waves might be responsible for how our innate immune response spreads from cell to cell. Viruses spread from cell to cell through trigger waves, so it makes sense that our initial line of immune defense might employ the same tactic.

"We have all this information on proteins and genes in all sorts of organisms, and we're trying to understand what the recurring themes are," Ferrell said. "We show that long-range communication can be accomplished by trigger waves, which depend on things like positive feedback loops, thresholds and spatial coupling mechanisms. These ingredients are present all over the place in biological regulation. Now we want to know where else trigger waves are found."

Ferrell is a member of Stanford's Bio-X and the Stanford Cancer Institute.

The study was funded by the National Institutes of Health.

Stanford's departments of Chemical and Systems Biology and of Biochemistry also supported the work. ISM

Autism

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region could prove therapeutic in ameliorating the social deficits of these neuropsychiatric disorders.

The Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, Malenka is the senior author of the study, whose findings were published online Aug. 8 in *Nature*. The lead author is postdoctoral scholar Jessica Walsh, PhD.

There are drugs called selective serotonin reuptake inhibitors, or SSRIs, that increase overall serotonin levels in the brain. But these widely used antidepressants take weeks to have a therapeutic effect and sometimes don't work at all — or eventually stop working. They haven't shown efficacy in countering autism spectrum disorder's social deficits, either.

'Turning on the faucet to maximum flow'

"SSRIs increase serotonin levels about as much as a moderately leaky faucet," Malenka said. "What we did in this series of experiments in mice was more like turning on that faucet to maximum flow." The researchers also tested the effects on mice's sociability of suddenly shutting off the faucet completely.

The nucleus accumbens, a midbrain structure found in all mammals, is a crucial hub of the brain's reward circuitry, which is a collection of brain areas whose networked activity makes us feel good about something we've done or are doing. This, in turn, instructs us to do more of it.

"Evolution has ensured that certain behaviors important for survival — eating, finding a mate, procreating, successfully escaping from predators or captivity — feel great," Malenka said.

In most mammals, social interaction sets off the reward circuitry, too. "Hanging out with your buddies makes sense from an evolutionary survival standpoint," Malenka said. "You're more likely to find a mate and less likely to be attacked." But people with autism spectrum disorder don't interact easily with others. They don't appear to experience the same rewarding sensation that people without these illnesses do.

In the new study, the scientists performed experiments that pinpointed the relevance of serotonin release in the nucleus accumbens to social activity in mice.

"Mice aren't little human beings," Malenka said. "We can't ask them how they're feeling about their social lives. But they provide insights into the human brain. They can be very useful for studying relatively primitive mechanisms governing social behavior. For example, if something makes a mouse want to spend more time with its buddies, that something is likely to be fun for the mouse."

Controlling cell signals with light

The scientists inserted genes encoding light-sensitive proteins into sets of nerve cells in the mice's brains. The scientists could now stimulate these nerve cells to fire impulses, or inhibit them from firing, with laser light delivered by an optical fiber implanted in the animals' brains.

First, Malenka and his colleagues sensitized nerve cells to light in another brain area called the dorsal raphe. This structure, the brain's main source of serotonin, sends nerve-cell projections to many brain areas, including the nucleus accumbens. Then the scientists put mice in situations in which they could choose to socialize or not. Activating nerve cells in the dorsal raphe made the mice more sociable.

Next, some mice were bioengineered so that only serotonin-secreting nerve cells running from the dorsal raphe to the nucleus accumbens were responsive to light. The scientists focused laser light on the nucleus accumbens, causing just the serotonin-secreting nerves there to release the substance — and inducing the same increased sociability. This experimental step ruled out involvement of other types of nerve cells in the tract from the dorsal raphe.

> "Hanging out with your buddies makes sense from an evolutionary survival standpoint."

But activating this circuitry didn't make the mice more inclined to move around or explore inanimate objects, or increase their interest in food. Serotonin release in the nucleus accumbens appears to reinforce only social behavior in the animals, Malenka said, making potential drugs that mimic or enhance this local release less likely to produce unwanted behaviors, such as drug addiction, overeating and excessive gambling.

Inhibiting rather than activating serotonin release in the nucleus accumbens dramatically reduced the sociability of normally friendly mice. This indicated that serotonin release in the nucleus accumbens plays an important role in the mice's normal social behavior.

To explore the possible connection between faulty serotonin-release circuitry in the nucleus accumbens and neuropsychiatric social deficits, the scientists zeroed in on one particular version of the more than 10 different known subtypes of receptors for serotonin. This version, called 5HT-1b, is a major subtype found in the nucleus accumbens. Drugs targeting 5HT-1b might produce fewer side effects than drugs with more general serotonin-circuitry effects.

Malenka's group next turned to mouse models of autism. The scientists deleted a specific chunk of genetic material from a chromosome in these mice to mimic an effectively identical genetic deletion in humans that accounts for about 1 percent of all clinically diagnosed cases of autism spectrum disorder. In mice, deleting this DNA either in nerve cells throughout the brain or only in serotonin-secreting nerve cells from the dorsal raphe produced social deficits in the mice that resemble some of those associated with its human counterpart.

The researchers found that this mutation significantly weakened serotonin-secreting activity in the nerve cells originating in the dorsal raphe, in a manner reminiscent of the direct inhibition of serotonin-secreting nerve cells that caused social deficits in normal mice. By using light to directly force those nerve cells' release of serotonin in the nucleus accumbens, the researchers could restore normal social behavior in the mouse models of autism. They were also able to restore normal sociability by infusing a drug that directly targets and activates 5HT-1b receptors in the nucleus accumbens, a result suggesting similar drugs might be beneficial in treating social behavior deficits.

Malenka expressed surprise at the consistency and strength of the study's results. "They couldn't have come out any better if I'd made them up," he said. "Usually you see some variability — some mice are having a bad hair day, others are having a good hair day. This time, we got similar results in almost every single animal we tested."

Malenka is deputy director of the Stanford Neurosciences Institute and a member of Stanford Bio-X.

Other Stanford co-authors of the study are postdoctoral scholar Daniel Christoffel, PhD; former life science research associate Gabriel Ben-Dor; former graduate student Aslihan Selimbeyoglu, PhD; former postdoctoral scholar Lin Hung, PhD; Boris Heifets, MD, PhD, clinical assistant professor of anesthesiology, perioperative and pain medicine; and Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences.

The work was funded by the Simons Foundation Autism Research Initiative and the National Institutes of Health.

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

5 QUESTIONS

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

How research is making MRI scans safer for kids

When it comes to medical imaging, pediatric radiologist and biomedical engineer Shreyas Vasanawala knows that kids aren't the same as adults.

Vasanawala, MD, PhD, professor of radiology at the School of Medicine, has spent the last 10 years studying how to improve magnetic resonance imaging scans for his smallest, wiggliest patients. Now, he's putting his MRI innovations to work in the Cynthia Fry Gunn and John A. Gunn Imaging Center at the new Lucile Packard Children's Hospital Stanford, which opened in December.

Vasanawala talked with science writer Erin Digitale about the needs that spurred his inventions and how the new hospital's state-of-the-art technology will improve his team's ability to care for children who need medical scans.

1 MRI scans are noninvasive, painless, don't use radiation and give clear images of soft tissues such as the liver, muscles and tendons, but children who could benefit from MRIs don't always get them. Why not?

VASANAWALA: Magnetic resonance technology is challenging to develop and use. Most of the MRI equipment on the market was designed to meet the needs of adult patients, who receive about 90 percent of MRI exams.

Shreyas Vasanawala

In an MRI scanner, the body is exposed to a very strong magnetic field. The protons in the body's water molecules align themselves with the magnetic field. We then manipulate them to make them give off radio-frequency signals that are detected by the scanner and translated into a picture.

To produce a clear picture, a traditional MRI scan requires that patients hold very still, sometimes for more than an hour. That's difficult for young children. Children are also smaller, breathe faster and have higher heart rates — all factors that make the imaging challenges harder from a physics perspective. Kids may be given anesthesia to help them hold still, but that carries its own risks.

Instead, many children receive computed tomography scans, which use powerful X-rays that carry a risk of cancer. Also, for many tissues, CT has less diagnostic power than MRI. We've been accepting a suboptimal imaging test for kids because it's more convenient, faster and doesn't require anesthesia.

2 As part of your research at Stanford, you've been designing MRI equipment especially for children. What improvements have you introduced?

VASANAWALA: We've invented solutions that have allowed us to eliminate the need for anesthesia in many cases and decreased the depth and duration of anesthesia in others.

We've been collaborating with engineers from UC-Berkeley to create new designs and production methods for highly flexible and lightweight MRI signal-receiving coils tailored to children's bodies. Standard coils are larger than children need, making them unnecessarily heavy and uncomfortable. Larger-than-necessary coils also pick up extra noise or interference, reducing the image quality. Child-size receiver coils increase image clarity and lower scan times.

The smaller coils also greatly enhance the performance of a novel hybrid-imaging technology called PET-MR, which we are now offering to patients in our new imaging center at Packard Children's Hospital. And the coils are being developed commercially as well.

3 How might these smaller receiver coils also help adult patients?

VASANAWALA: There is a whole host of potential applications for adults. Sometimes you can see a lesion on an MRI that you want to biopsy but can't reach when the area is covered with a big, bulky coil. With the lower-profile equipment, we'll be able to biopsy through holes in the coil. Also, a light flexible coil is just more comfortable for everyone.

And not every adult is a thin 6-foot male. The new equipment will help us meet more patients' needs. For instance, for breast MRI, it's very helpful to have a form-fitting coil that sits close to the lesions we're trying to image.

4 You've also improved the computing software that processes MRI data. How?

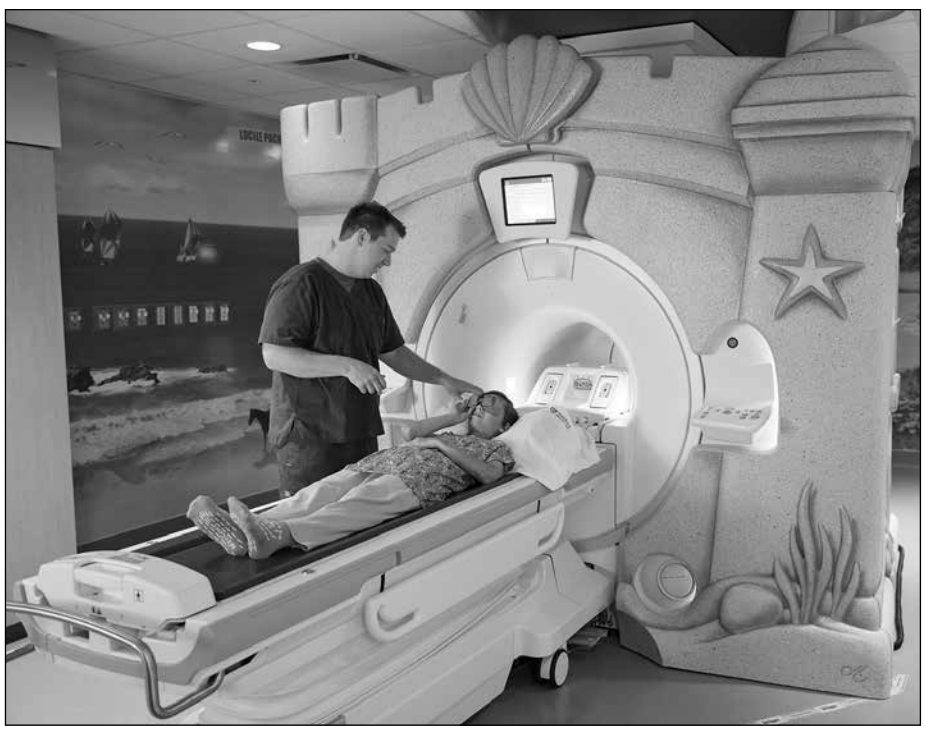
VASANAWALA: Joseph Cheng, PhD, an electrical engineer in our group, has taken the lead in creating new image-reconstruction algorithms that work better for kids. We deployed motion-correction strategies that produce sharp images even when a child is moving slightly — this helps address the challenge of kids' faster heart rates and breathing rates. Simultaneously, to reduce scan times, we implemented novel, high-dimensional imaging and compressed sensing coupled with artificial intelligence. These techniques allow the computer to reconstruct a full MR image from much less raw data. Scans that once took an hour are now complete in 5-10 minutes. This has had a particularly large impact for our cardiac, oncologic and musculoskeletal exams.

5 What most excites you about in the new imaging center at Packard Children's?

VASANAWALA: For the first time, we have an MRI scanner located inside our neurosurgery operating suite. It allows our neurosurgeons to confirm the success of a surgical procedure, such as a tumor resection, before surgery is complete. This saves time by eliminating a separate post-surgical MRI and the risk of needing an immediate repeat surgery. Patients will be spared a second round of anesthesia, hospital stays will be shortened and families will know if the surgical aims have been achieved as soon as their child is out of the operating room.

By the end of 2019, we will have a next-generation MRI scanner with much stronger magnetic field gradients that can be altered at high speed. This enables faster imaging and better image contrasts. Also, this new MRI scanner will come with a noninvasive technology used to kill certain types of tumors using sound waves. Known as MR-guided high-intensity focused ultrasound, it lets us pinpoint abnormal areas in the body, such as some types of tumors, and heat them to destroy the abnormality without cutting into surrounding healthy tissue. **ISM**

COURTESY OF LUCILE PACKARD CHILDREN'S HOSPITAL



The facade of an MRI machine at Packard Children's Hospital was made to resemble a sandcastle.

Cancer

continued from page 1

avoid sun exposure, which is why proteins that repair DNA damage are important to prevent skin cancers like basal cell carcinoma.

Kavita Sarin

Most of the time this system works well. But sometimes the repair team can't keep up. Basal cell carcinomas are common — more than 3 million cases a year are diagnosed in the United States alone — and usually highly treatable.

Sarin and Cho wondered whether the skin could serve as a kind of canary in the coal mine to reveal an individual's overall cancer susceptibility. "The skin is basically a walking mutagenesis experiment," Sarin said. "It's the best organ to detect genetic problems that could lead to cancers."

Sarin and Cho studied 61 people treated at Stanford Health Care for unusually frequent basal cell carcinomas — an average of 11 per patient over a 10-year period. They investigated whether these people may have mutations in 29 genes that code for DNA-damage-repair proteins.

"We found that about 20 percent of the people with frequent basal cell carcinomas have a mutation in one of the genes responsible for repairing DNA damage, versus about 3 percent of the general population. That's shockingly high," Sarin said.

Furthermore, 21 of the 61 people reported a history of additional cancers, including blood cancer, melanoma, prostate cancer, breast cancer and colon cancer — a prevalence that suggests the frequent basal cell carcinoma patients are three times more likely than the general population to develop cancers.

'A strong correlation'

To confirm the findings, the researchers applied a similar analysis to a large medical insurance claims database. Over 13,000 people in the database had six or more basal cell carcinomas; these people also were over three times more likely to have developed other cancers, including colon, melanoma and blood cancers. Finally, the researchers identified an upward trend: the more basal cell carcinomas an individual reported, the more likely that person was to have had other cancers as well.

"I was surprised to see such a strong correlation," Sarin said. "But it's also very gratifying. Now we can ask patients with repeated basal cell carcinomas whether they have family members with other types of cancers, and perhaps suggest that they consider genetic testing and increased screening."

The researchers are continuing to enroll Stanford patients in the study, which is ongoing, to learn whether particular mutations in genes responsible for repairing DNA damage are linked to the development of specific malignancies. They'd also like to conduct a similar study in patients with frequent melanomas. But they emphasized that there's no reason for people with occasional basal cell carcinomas to worry.

> "About 1 in 3 Caucasians will develop basal cell carcinoma at some point in their lifetime."

"About 1 in 3 Caucasians will develop basal cell carcinoma at some point in their lifetime," Sarin said. "That doesn't mean that you have an increased risk of other cancers. If, however, you've been diagnosed with several basal cell carcinomas within a few years, you may want to speak with your doctor about whether you should undergo increased or more intensive cancer screening."

Other Stanford authors of the study are former dermatology resident Karen Kuo, MD; statistical programmer Shufeng Li; clinical research coordinator Irene Bailey; clinical professor of dermatology Sumaira Aasi, MD; associate professor of dermatology Anne Chang, MD; professor of dermatology Anthony Oro, MD, PhD; and professor of dermatology Jean Tang, MD, PhD.

The study was supported by the Dermatology Foundation, the National Institutes of Health, the Stanford Society of Physician Scholars, the American Skin Association and Pellepharm Inc.

Tang and Epstein are co-founders, directors and officers of Pellepharm, a biotechnology company focused on rare dermatological conditions.

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

New imaging technique can spot tuberculosis infection in an hour

By Hanae Armitage

Guided by glowing bacteria, researchers have devised an imaging technique that can diagnose live tuberculosis in an hour and help monitor the efficacy of treatments. That's particularly critical because many TB strains have evolved defenses against standard treatments.

Jianghong Rao, PhD, a professor of radiology at the School of Medicine, said speedy TB diagnostics are sorely needed, as current methods can take up to two months to complete — a stretch during which infected individuals could spread the disease broadly, even if they don't know they're infected. A quicker diagnosis could curtail the infection rate.

What's more, the new method is cheaper and easier to carry out, ideally enabling health care providers in poorer communities to one day adopt the technology.

A paper describing the research was published Aug. 15 in Science Translational Medicine. Rao is the senior author. The lead author is research scientist Yunfeng Cheng, PhD.

To diagnose TB, clinicians need to collect a sample of sputum, the coughed-up stuff also known as phlegm; cultivate it in the lab; and wait for the bacteria to grow to detectable level. It also requires specialized facilities, which are missing in many hospitals worldwide.

"In still-developing countries where TB is most prominent, it's hard to maintain those kinds of intensive facilities, and it can be expensive," Rao said.

The new imaging technique uses run-of-the-mill fluorescence microscopes that nearly all hospitals have and that require no special training, he said. All that's needed is a sample of the patient's sputum that can be prepared and put under the microscope for analysis.

The tactic harnesses a newly created two-piece fluorescent probe, which Rao likens to a lamp. The probe is combined with the sputum sample and gets activated, or switched on, when it comes in contact with TB bacteria. One part of the probe is responsible for detecting live TB, thus creating the telltale glow; the second part, a molecule that binds specifically to the TB microbe, localizes the glow to the bacterium. The concentrated fluorescence allows scientists to not only see the rod-shaped bacteria themselves, but also to track their distribution in infected host cells.

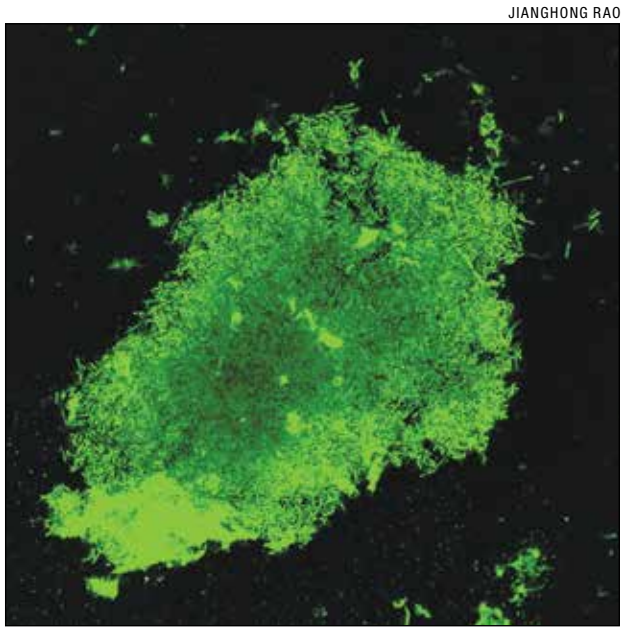
"For cases of drug-susceptible TB, the treatment success rates are at least 85 percent, but the rate of success is only 54 percent for multidrug-resistant TB, which requires longer treatments and more expensive, more toxic drugs," Rao said.

The fluorescent probe, Rao said, can help determine the appropriate drug by literally showing which bacteria are still alive in the patient sample: Those that are alive glow green; those that aren't (or are a different species of bacteria) appear dark.

Outside the clinic, Rao said the technique could help scientists developing new TB drugs figure out which drugs work best for each particular strain. Now, Rao and his colleagues are planning to test the probe and to work on obtaining approval from the Food and Drug Administration.

"The hope is to make this an adaptable technology," Rao said. "It's something that could be really widespread, and you wouldn't necessarily need to use it in a hospital setting." ISM

JIANGHONG RAO



Researchers applied the fluorescent probe to a sputum sample collected from a TB-positive patient. The bright green shows where there is live TB.

OF NOTE

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

Nima Aghaeepour

Sundari Chetty

Ngan Huang

Laura Johnston

Kevin Shea

NIMA AGHAEEPOUR, PhD, was appointed assistant professor (research) of anesthesiology, perioperative and pain medicine, effective April 1. His research focuses on using machine learning, such as integrative analysis across genomics, proteomics and single-cell technologies, as well as quantitative clinical phenotyping, to study the immune system in clinical settings.

SUNDARI CHETTY, PhD, was appointed assistant professor of psychiatry and behavioral sciences, effective June 1. Her research focuses on understanding the mechanisms that regulate how human pluripotent stem cells differentiate into specialized cells, with the goal of improving cell replacement therapy and disease modeling.

NGAN HUANG, PhD, assistant professor of cardiothoracic surgery, received a $300,000 grant from the National Science Foundation. The three-year grant will support her work sending engineered muscle tissue to the International Space Station for drug testing in microgravity. Because muscle breaks down more quickly in a microgravity environment, the goal is to test whether bioengineered muscle in the space station undergoes muscle wasting, and then to use this setting for screening drug treatments for such muscle-wasting diseases as sarcopenia.

LAURA JOHNSTON, MD, was promoted to professor of medicine, effective June 1. She is the clinical director and clinic chief of the Blood and Marrow Transplantation Division. Her research focuses on prevention and treatment of graft-versus-host disease, as well as on understanding patient characteristics and comorbidities that may affect transplant outcomes.

KEVIN SHEA, MD, was appointed professor of orthopaedic surgery, effective July 1. His research interests include 3-D modeling of pediatric knee anatomy for surgery, cartilage and ligament reconstruction, and reducing variation in care through the use of clinical practice guidelines.

KATHERINE WANG, MD, a postdoctoral scholar in nephrology, has been named the Clinical Scientist in Nephrology fellow for 2018-19 by the American Kidney Fund. The $80,000 grant will fund her research on the effects of intensive treatment of hypertension in patients with chronic kidney disease and the factors associated with the inability to achieve lower systolic blood-pressure targets. ISM

Katherine Wang

Three faculty members appointed to endowed positions

TERI LONGACRE, MD, professor of pathology, was appointed the Richard L. Kempson, MD, Professor of Surgical Pathology, effective June 14. Her research and clinical interests include gynecological and gastrointestinal pathology, with a specialty in hereditary cancer syndromes. The professorship was established in 2002.

Kempson is a professor emeritus of pathology who specialized in gynecological pathology and co-founded the surgical pathology laboratory at Stanford Hospital.

JOHN SUNWOO, MD, professor of otolaryngology-head and neck surgery, was appointed the Edward C. and Amy H. Sewall Professor, effective June 14. He investigates the interactions between the immune system and head and neck cancers, with a particular focus on the role of natural killer cells.

The professorship is the fifth established with funds from the late Edward and Amy Sewall. Edward Sewall was a professor at Cooper Medical College in San Francisco, which became the medical department for Stanford. He was later a chief of otolaryngology and a professor of surgery, emeritus, until his death in 1957.

ROELAND NUSSE, PhD, professor of developmental biology, was appointed the Reed-Hodgson Professor of Human Biology, effective Sept. 1. His research examines the role of the signaling molecule Wnt, which is involved in embryonic development, cancer and functions of adult stem cells.

The late Richard Hodgson and his wife, Geraldine Coursen Reed, graduated from Stanford in the late 1930s and supported Stanford throughout their lives. Hodgson was a co-founder and director of Intel Corp. he served as an executive at International Telephone and Telegraph Corp., as well as several other technology companies. ISM

Teri Longacre

John Sunwoo

Roeland Nusse