INSIDE STANFORD MEDICINE

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Researchers mapped a network of gene activity before and after heart failure to better understand how heart health declines.

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# Cancer prognostics takes page from sports

By Krista Conger

In this season of global soccer competitions and hotly contested political primaries, bookies and pundits are scouring every evolving scrap of information and sifting through mountains of data in an effort to predict the outcome of the next game or election. These predictions can change on a dime, however, based on a player's poor pass or a candidate's stellar debate performance.

Statisticians refer to the technique of incorporating a variety of continuously generated information — who is on the bench, who was injured in the first half of the match, who polled well in Iowa yesterday — as calculating in-game win probability, and it's been used for decades to predict the outcome of ongoing sports matches or elections.

Now, researchers at the School of Medicine have taken a page from this playbook to generate more accurate prognoses for cancer patients. They've done so by designing a computer algorithm that can integrate many different types of predictive data — including a tumor's response to treatment and the amount of cancer DNA circulating in a patient's blood during therapy — to generate a single, dynamic risk assessment at any point in time during a patient's course of treatment. Such an advance could be deeply meaningful for patients and their doctors.

"When we care for our patients, we are walking on eggshells for a profound period of time while we try to determine whether the cancer is truly gone, or if it is likely to return," said associate professor of medicine Ash Alizadeh, MD, PhD. "And patients are wondering 'Should I be planning to attend my child's wedding next summer, or should I prioritize making my will?' We are trying to come up with a better way to predict at any point during a patient's course of treatment what their outcome is likely to be."

Surprisingly, the researchers have also found that the approach, which they've termed CIRI for continuous individualized risk index, may also help doctors to pinpoint people who might benefit from early, more aggressive treatments as well as those who are likely to be cured by standard methods.

The study was published online July 4 in *Cell*. Alizadeh, a Stanford Health Care oncologist who specializes in treating patients with blood cancers, shares senior authorship with associate professor of radiation oncology Maximilian Diehn, MD, PhD. Instructor of medicine David Kurtz, MD, PhD, and postdoctoral scholars Mohammad Esfahani, PhD, and Florian Scherer, MD, are the lead authors.

### Getting a more complete picture

The researchers began their study by looking at people previously diagnosed with diffuse large B-cell lymphoma, which is the most common blood cancer in the United States. Although nearly two-thirds of adults with DLBCL are cured with standard treatment protocols, the remaining third will likely die from the disease.

When a DLBCL patient See CANCER, page 6

MARK TUSCHMAN

Maximilian Diehn and Ash Alizadeh and their team have devised a way to better predict a cancer patient's outcome during treatment.

# Stroke damage in mice shrunk by quieting certain immune cells outside brain, new study reports

By Bruce Goldman

Investigators at the School of Medicine have shown that suppressing the activity of a small set of immune cells in mice after they've had a stroke substantially reduces their brain damage, boosts their survival rate and improves their motor performance days later.

The findings suggest that selectively subduing these immune cells, which migrate to the brain after a stroke, could meaningfully treat the stroke even days after it takes place, said Katrin Andreasson, MD, professor of neurology and neurological sciences.

Such an approach may be preferable because the immune cells in question uniquely express, on their surfaces, a molecule that acts as an inflammatory loudspeaker. Turning down its volume softens the inflammatory disposition of the immune cells.

A paper describing the study was published online July 1 in *Nature Immunology*. Andreasson is the senior author. The lead author is postdoctoral scholar Qingkun Liu, PhD.

STEVE FISCH

Katrin Andreasson is the senior author of a study that found suppressing certain immune cells reduced brain damage in mice that had a stroke.

"This new approach worked," Andreasson said. "It might mean we can prevent a lot of the brain damage and functional losses that occur after a stroke just by targeting the immune response instead of damaged nerve cells or blood vessels."

In the aftermath of a stroke, the brain is invaded by activated immune cells, whose activity peaks about two days after the stroke and continues to rage for a few more days after that. The new study examined mice whose blood flow in a cerebral artery See STROKE, page 7

OBITUARY

# Christopher Dawes, former CEO of Packard Children's Hospital, dies at 68

By Ruthann Richter

Christopher Dawes, who served as chief executive officer of Lucile Packard Children's Hospital Stanford for 18 years, died June 29 of amyotrophic lateral sclerosis, also called Lou Gehrig's disease. He was 68.

Dawes guided the hospital during its formative years, building it into a nationally renowned center for advanced children's care. He was beloved by the hospital community for his steady leadership, his warmth and humble nature, his passionate advocacy for children's health, and his ability to listen to those around him as he implemented bold initiatives to build an outstanding enterprise.

As CEO, he directed a $500 million program to build world-class centers of excellence in several medical specialties; developed a comprehensive, regional network of care for children and mothers; and oversaw a significant expansion of the hospital into a new, technologically advanced, 361-bed facility that opened in 2017.

"We went from being a very lovely community hospital, nicely designed and family-friendly, to a world-class children's hospital drawing patients from across the United States and around the world," said Susan Packard Orr, a longtime member of the hospital's board of directors and daughter of hospital founder, Lucile Packard.

Dawes oversaw the transformation in his characteristically understated way, she said. "He was just a very gentle, low-key guy," Orr said. "He was a fabulous manager and knew how to hire the right people and motivate them to do good work. A hospital is a really complicated business, and he See DAWES, page 7

STANFORD CHILDREN'S HEALTH

Christopher Dawes guided the hospital during its formative years, building it into a nationally renowned center for advanced children's care.

# Neural sleep patterns emerged at least 450 million years ago

**By Mandy Erickson**

Researchers at the School of Medicine have found that neural signatures in sleeping zebrafish are analogous to those of humans, suggesting that the brain activity evolved at least 450 million years ago, before any creatures crawled out of the ocean.

Scientists have known for more than 100 years that fish enter a sleeplike state, but until now they didn't know if their sleep resembled that of land animals.

The researchers found that when zebrafish sleep, they can display two states that are similar to those found in sleeping mammals, reptiles and birds: slow-wave sleep and paradoxical, or rapid eye movement, sleep. The discovery marks the first time these brain patterns have been recorded in fish.

"This moves the evolution of neural signatures of sleep back quite a few years," said postdoctoral scholar Louis Leung, PhD.

A paper describing the research was published July 10 in *Nature*. Philippe Mourrain, PhD, associate professor of psychiatry and behavioral sciences, is the senior author. Leung is the lead author.

KAZAKOV MAKSIM/SHUTTERSTOCK.COM

Scientists found that when zebrafish sleep, they can display two states similar to those found in sleeping mammals, reptiles and birds.

To study the zebrafish, common aquarium dwellers also known as danios, the researchers built a benchtop fluorescent light-sheet microscope capable of full-fish-body imaging with single-cell resolution. They recorded brain activity while the fish slept in an agar solution that immobilized them. They also observed the heart rate, eye movement and muscle tone of the sleeping fish using a fluorescence-based polysomnography that they developed.

Philippe Mourrain

They named the sleep states they observed "slow bursting sleep," which is analogous to slow-wave sleep, and "propagating wave sleep," analogous to REM sleep. Though the fish don't move their eyes during REM sleep, the brain and muscle signatures are similar. (Fish also don't close their eyes when they sleep, as they have no eyelids.)

### Sleeping like the fish

The researchers found another similarity between fish and human sleep. By genetically disrupting the function of melanin-concentrating hormone, a peptide that governs the sleep-wake cycle, and observing neural expressions as the fish slept, the researchers determined that the hormone's signaling regulates the fish's propagating wave sleep the way it regulates REM sleep in mammals.

Other aspects of their sleep state are similar to those of land vertebrates, Mourrain said: The fish remain still, their muscles relaxed, their cardio-respiratory rhythms slow down and they fail to react when they're approached.

"They lose muscle tone, their heartbeat drops, they don't respond to stimuli — the only real difference is a lack of rapid eye movement during REM sleep," Mourrain said, though he added, "The rapid movement of the eyes is not a good criterion of this state, and we prefer to call it paradoxical sleep, as the brain looks awake while one is asleep."

While scientists can't say for certain that all animals sleep, it appears to be a universal need among vertebrates and invertebrates. Animals will die if they are deprived of sleep long enough, and people who fail to receive adequate sleep suffer from mental problems such as memory lapses and impaired judgment, along with a higher risk of disorders such as obesity and high blood pressure.

The exact benefits of sleep are still a mystery, however. "It's an essential function," Mourrain said, "but we don't know precisely what it does."

He added that sleep disorders are linked to most neurological disorders such as autism spectrum disorders, Fragile X syndrome, and Alzheimer's and Parkinson's disease. "Sleep disturbances are an aggravating factor of these disorders," Mourrain said. It is critical to develop this animal model to study sleep functions at the cellular level, including neuronal connectivity and DNA repair, and in turn understand the pathophysiological consequences of sleep disruptions, he added.

The discovery means sleep research can be conducted on zebrafish, which are easy to study, in part because they're transparent. They breed quickly, are inexpensive to care for and are just over an inch long. Drug testing requires only the addition of chemicals to their water.

"Because the fish neural signatures are in essence the same as ours, we can use information about them to generate new leads for drug trials," Leung said. He added that mice, often a stand-in for human research, are nocturnal and a less relevant model for our sleep.

"As zebrafish are diurnal like humans, it's perhaps more biologically accurate to compare fish sleep with humans for some aspects," Leung said. **ISM**

# U.S. foreign policy restricting abortion funding results in more abortions

**By Krysten Crawford**

A U.S. foreign policy that cuts money to nongovernmental organizations performing or promoting abortions abroad has actually led to an increase in abortions, according to Stanford researchers who have conducted the most comprehensive academic study of the policy's impact.

Eran Bendavid, MD, and Grant Miller, PhD — both associate professors of medicine at the School of Medicine — and graduate student Nina Brooks found that abortions increased among women in African countries where NGOs, such as the International Planned Parenthood Federation, were particularly vulnerable to the policy's requirements.

The policy, widely known as the Mexico City Policy, explicitly prohibits U.S. foreign aid from flowing to any NGO that does not agree to abide by the policy's main condition: no performing or discussing abortion as a method of family planning, even if just in the form of education or counseling.

The policy has been a political hot potato since its inception. Enacted under Ronald Reagan in 1984, it's been enforced by subsequent Republican administrations, whereas Democrats in the White House have revoked the policy within days of taking office.

The study, published June 27 in *The Lancet Global Health*, looked at the policy's effects in more than two-dozen African countries over a span of 20 years under three presidents: Bill Clinton, George W. Bush and Barack Obama. It found that, when the policy was in place during the Bush years, abortions were 40 percent higher relative to the Clinton and Obama administrations.

When the policy was suspended during Obama's two terms, the Stanford researchers found that the upward trend in abortion rates reversed.

"Our research suggests that a policy that is supported by taxpayers ostensibly wishing to drive down abortion rates worldwide does the opposite," Bendavid said.

MARIE STOPES INTERNATIONAL

Women in rural Zimbabwe attend a contraceptive education session run by Marie Stopes International.

A key reason for the uptick in abortions is that many NGOs affected by the policy also provide contraceptives — and funding cuts means birth control is harder to get, Brooks said.

"By undercutting the ability to supply modern contraceptives, the unintended consequence is that abortion rates increase," she said.

The policy's scope has expanded under the Trump administration. While it originally restricted aid directed only toward organizations providing family planning and reproductive health services, President Trump has extended the policy to cover any group engaged in global health, including organizations providing services for HIV or child health — not just family planning.

### Groundbreaking research

The stakes are high. America is the world's largest provider of development assistance: It spent about $7 billion on international health aid in 2017. Many women in sub-Saharan Africa depend on this aid for contraceptives.

In sub-Saharan Africa, NGOs are often primary providers of family planning services. Two of the world's largest family planning organizations, International Planned Parenthood Federation and Marie Stopes International, have forfeited large sums from the U.S. government for refusing to comply with the policy, according to news reports.

The research findings were based on records of nearly 750,000 women in 26 sub-Saharan African countries from 1995 to 2014. When the policy was in effect under George W. Bush, contraceptive use fell by 14 percent, pregnancies rose by 12 percent and abortions rose by 40 percent relative to the Clinton and subsequent Obama years — an impact sharply timed with **See ABORTION, page 3**

INSIDE STANFORD MEDICINE

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STANFORD MEDICINE

5 QUESTIONS

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

# Wojcik on need for diversity in genome studies

*If you've ever had genetic testing done, you might have noticed a few lines of fine print in the accompanying paperwork acknowledging that the results may not accurately represent individuals of non-European descent. That's not unusual, said Genevieve Wojcik, PhD, a postdoctoral scholar at the School of Medicine who studies biomedical data science, but it is a problem.*

*This caveat is often seen in something called a genomewide association study, or GWAS, which harnesses technology to read DNA and look for genetic variants that show up in association with specific diseases. The idea is to look at the DNA of a population and spot common variants that seem to correspond to an illness, such as heart disease, cancer or diabetes. But giving these studies the power they need to uncover these links requires data from thousands of individuals.*

*The problem, Wojcik said, is that often the available genetic data comes from individuals of European descent, and results from one racial or ethnic group don't always apply to another. In a study published June 19 in* Nature*, Wojcik and her colleagues dig into that problem and show how diversity in genetic analyses improves our understanding of complex traits and disease risk.*

*Science writer Hanae Armitage spoke with Wojcik about the study, discussing the lack of diversity in GWAS research, how diversity can elevate it and what scientists can do to better include a broad range of populations when conducting these kinds of genomic analyses.*

### 1 What are a couple of key factors behind the lack of diversity in genomewide association studies?

**WOJCIK:** A GWAS requires a large number of samples to get a strong signal, and a lot of the large cohorts and health-related studies are done in groups that are mostly of European descent. This is for a variety of reasons, including patient participation, the geographic location of these studies and the overall recruitment efforts.

Historically, genomic studies tended to favor somewhat homogenous populations to minimize confounding factors and make sure that any signal you pick up on is genuine. So scientists would often organize their studies by the different racial or ethnic groups, and the European-descent group was usually the largest. Eventually, that became the norm since there was simply more data. But now things are changing. We have much larger studies occurring in metropolitan areas and on a national level with more diverse populations. We also have computational methods that help us analyze less-homogeneous data more effectively, and we can gain more information by having everyone together versus focusing on the largest group.

Genevieve Wojcik

### 2 Why is it important to increase diversity in genetic studies?

**WOJCIK:** If a GWAS only incorporates data from one racial or ethnic group, the results are typically most applicable to that one population. The effect of that variant in other groups may be smaller or nonexistent. Non-European descent groups have a disproportionately higher burden of disease, especially in the United States. When GWASes focus on data from just individuals of European descent, you can exacerbate that disparity. That's one of the things we're trying to address by having diverse groups in our genomic analyses. By increasing minority representation, you're ensuring that these groups don't get left behind.

### 3 What is the PAGE study and how is it different from most genomewide studies?

**WOJCIK:** The PAGE study, which stands for Population Architecture Using Genomics and Epidemiology, was originally developed by the National Human Genome Research Institute in an effort to address the very problem we've been talking about: A large majority of genomic research is done in European-descent groups.

The PAGE study is bringing together numerous institutes and existing studies to pool genomic data from individuals who have historically been sidelined in genomewide association studies — namely, racial and ethnic minorities. The study's overall goal is to investigate a diverse population to better understand how genetic factors affect susceptibility to disease. PAGE has been around for about a decade, and their recent focus has been on gathering and analyzing gene information from 50,000 individuals of non-European descent. Our role at Stanford is to help coordinate and analyze the data.

### 4 How does a diverse cohort add to the power of a genomewide screen?

**WOJCIK:** Variants in or near genes can be associated with risk for a particular condition; that's why we do GWASes. But it's not always clear-cut. For instance, a GWAS usually points to several variants within one gene that all seem to correspond to that particular condition. Adding more diverse data can actually help zero in on which variants are most likely to be causal for the condition, and which just coincidentally pop up in our GWASes because they are nearby. We demonstrated this using data from the PAGE study, in which we looked at genetic associations with height. We already had a lot of data from a previous GWAS of 250,000 people, who were predominantly of European-descent. For one of the identified genes, there were four genetic variants associated with height, but we weren't able to narrow it down to the likely causal variant. We tried adding data from another 50,000 European-descent participants, but still weren't able to narrow down our list. But when we added genomic data from the 50,000 multi-ethnic participants from the PAGE study, we found that there was only one genetic variant that was consistently involved with height.

### 5 What can researchers do to ensure that their genetic studies are more diverse and inclusive?

**WOJCIK:** I think first and foremost, there needs to be a shift in mindset. In addition to the social justice merits of this work, there's true scientific cause for increasing diversity in GWASes. This paper does a great job of laying down a framework to show that. We're saying, "You really have no excuse; look at the scientific rationale for including diverse groups in genomic studies. Just because it's harder to include broad diversity doesn't mean you don't have to do it."

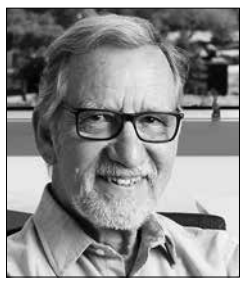
Pooling data from diverse groups actually enhances precision in disease risk predictions or associations when properly analyzed. Nowadays, we have computer methods that can handle immense complexity in your data, so it actually doesn't always make a whole lot of sense to run separate GWASes for different populations. Genetic diversity is a spectrum, not a box you check on a survey, and it's crucial that we adjust our approach to genomic studies to treat it as such. **ISM**

# Stanford-led team receives $10 million award for myosin research

**By Bruce Goldman**

The National Institute of General Medical Sciences has awarded a five-year, $10 million grant to a multidisciplinary, multi-institutional team of scientists led by School of Medicine researchers that will try to gain insights into a common cause of heart failure.

The lead Stanford researchers are James Spudich, PhD, professor of biochemistry; Daniel Bernstein, MD, professor of pediatrics; and Sean Wu, MD, PhD, associate professor of cardiovascular medicine. Co-investigators are Alexander Dunn, PhD, associate professor of chemical engineering, and Kathleen Ruppel, MD, senior scientist in biochemistry.



James Spudich

The Stanford-led team — which also includes researchers from the University of California-Santa Barbara, the University of Washington and the Institut Curie in Paris — will seek a deep understanding of exactly how minute changes within genes, and the resulting alterations in the proteins for which those genes are recipes, can give rise to complex disease profiles.

The grant came about as the result of a national competition, with each institution limited to a single submitted application. This granting mechanism was initiated in 2017 with the express intent, according to the NIGMS, of supporting projects that "address complex and challenging biomedical problems." Spudich and Bernstein's proposed project was selected through an internal review process that took place at Stanford. It was one of only three such proposals the NIGMS selected this fiscal year for grants totaling an estimated $27 million over a five-year period.

The team will focus on a particular protein, myosin, which is responsible for cell contraction in numerous tissues and organs, notably including skeletal muscle and the heart. Mutations in myosin have been implicated in a variety of cardiomyopathies, irregularities in heart-muscle function that affect 1 in every 500 people and are major causes of heart failure and sudden death. Myosin mutations can also cause skeletal muscle diseases that lead to impaired motor function.

Spudich is the Douglass M. and Nola Leishman Professor of Cardiovascular Disease. Bernstein is the Alfred Woodley Salter and Mabel G. Salter Endowed Professor in Pediatrics and the school's associate dean for curriculum and scholarship. The two scientists and their colleagues intend to develop a comprehensive understanding of how the hallmarks of various forms of cardiomyopathy can arise from minute, mutation-induced variations in individual myosin molecules. They will conduct their examination at several different scales, observing methodically how disease-causing alterations in myosin affect the structure and mechanical properties of the mutated protein and of the contractile subcellular entities of which it is a crucial component (subcellular entities of interest in the heart include repeating myosin-rich filamentous subunits called myofibrils).

The investigators will also introduce specific mutations to human induced pluripotent stem cells in order to monitor the resulting dysfunctions at the cell and tissue level, and they will develop computational models to extend their findings across a broad spectrum of contractile-protein mutations. **ISM**

## Abortion

**continued from page 2**

the policy and in proportion to the importance of foreign assistance across sub-Saharan Africa.

The paper is the second study of the rule's impact by Bendavid and Miller, and is also one of the few evidence-based analyses of the policy.

Their earlier research was the first quantitative, large-scale effort to examine the policy's impacts. It looked at a smaller set of African countries during the Clinton and Bush administrations and also found an increase in abortion rates when the policy was enacted in 2001.

"Our latest study strengthened our earlier findings because we were able to look at what happens when the rule was turned off, then on, and then off again," said Bendavid, referring to the policy's whipsawing under Clinton, Bush and then Obama.

Miller said the team's research reveals a deeply flawed policy.

"We set out to provide the best and most rigorous evidence on the consequences of this policy," he said. "What we found is a clear-cut case of government action that everyone on all sides of the abortion debate should agree is not desirable."

### Signs of global pushback

Brooks noted that the findings may underestimate the rule's full impact.

"The excess abortions performed due to the policy are more likely to be performed unsafely, potentially harming women beyond pregnancy terminations," she said.

Norway, Canada and several other countries have pledged to increase funding of international NGOs affected by the policy — though not by enough to cover the expected shortfall, Miller said.

"This shows us," he said, "that despite the intense partisanship in the U.S. over the rule and its implementation, there are ways that policymakers around the world can offset its effects — by ensuring higher levels of family planning funding, for example." **ISM**

# Gene networks reveal transition from healthy to failing heart

**By Hanae Armitage**

Scientists investigating heart failure have been limited to studying diseased heart tissue in the lab — understandably, as people don't tend to pluck out a healthy heart for the sake of research. But now, scientists with access to unusable, yet still healthy, donor hearts have been able to investigate the genomic pillars behind the transition from healthy hearts to heart failure.

In doing so, researchers at the School of Medicine and their collaborators have created one of the first maps to reveal gene activity and connectivity as the heart shuts down.

Euan Ashley, MB ChB, DPhil, professor of medicine, of genetics and of biomedical data science at Stanford, calls it a gene network. These networks, he said, are akin to social networks. "Let's say we traced the whereabouts of the human resources department at Stanford. We could see that they tend to park in the same area, go to the same office and get lunch in the same place," he said. "They move together, and so it can be reasonably inferred that they are somehow related to each other."

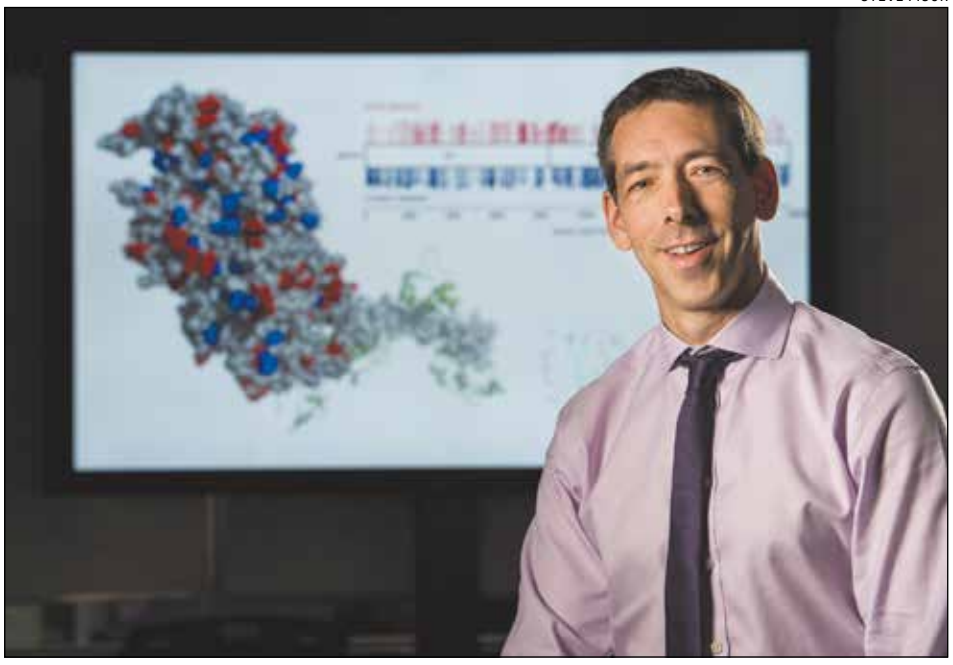
Tracing a gene network for heart failure is like that, only instead of watching physical movements, Ashley and his collaborators watched for changes in gene expression, paying attention to how it changes as healthy hearts degenerate.

By delineating these gene networks, the group has discovered one gene in particular that seems to be at the center of the action. It appears to be highly connected in heart failure, meaning its activity is similar to that of many neighbors. What's even more exciting, Ashley said, is that when the researchers disabled the function of this gene in mouse models of heart failure, the mice were protected and did not succumb to the cardiac condition.

"This study has a truly unique angle, which is that we had precious, healthy human tissue and we used it to tell us something new about how a disease manifests," said Victoria Parikh, MD, clinical instructor of cardiovascular medicine. "And now someday we might even be able to translate that into a treatment."

A paper providing details of the study was published June 24 in *Nature Communications*. Ashley is the senior author. Parikh shares lead authorship with Pablo Cordero, PhD, a former Stanford graduate student.

STEVE FISCH



Euan Ashley and his collaborators created a map of how genes network as the heart fails.

### Tracking the transition

Heart failure is not one simple condition, said Ashley. It's more like an umbrella term that describes the heart's inability to pump blood regardless of the cause. "It could be a heart attack, a genetic cause, high blood pressure, a valve problem or something else entirely," he said. "Regardless of how the heart deteriorates, we believe there's one final, common pathway that ultimately leads to heart failure."

> "This study has a truly unique angle."

Now, the web of genes that they've mapped is providing new insight into how that pathway unfolds, and which genes are crucial to its activation.

"Maybe someday we'll be able to peer into a cell and watch as the networks are actively changing in real time," Ashley said. "But right now what we have is human tissue that's sort of frozen at a moment in time, and so we can use that to look at which genes are involved in this process."

The group took tissue samples from more than 300 hearts (half from hearts removed from patients with heart failure who were getting heart transplants and half from healthy donor hearts) and ran genomic tests to determine gene expression activity. It was essential, Ashley said, to have the healthy donor hearts available. "Sometimes, for logistical reasons, a donor's heart isn't usable for transplantation, so instead of wasting these organs, we repurposed them for our study." Thanks to a dedicated, multi-institutional surgical team that worked around-the-clock — sometimes venturing out in the wee hours of night — the group secured more than 100 healthy hearts.

### A new target

To date, studies that compare the genomics of healthy hearts and heart failure have taken place mainly in mice. But with the healthy donor heart tissue, the team was able to compare and contrast genomic information in human hearts. They found that fewer biological pathways were involved in heart failure compared with healthy hearts, but there were more genes involved in those pathways. It's almost as if the cells were "focusing" their efforts**,** presumably as part of a last-ditch effort to restabilize the declining heart, said Ashley.

Perhaps most telling, PPP1R3A had one of the biggest leaps in gene connectivity during the transition to heart failure, meaning it became associated with the activity of many other genes. And although it hasn't been implicated in heart failure in the past, its role does seem to fit with some of the symptoms, Ashley said. The heart's energy source typically comes from fatty acids, but it switches to glucose when it goes into failure. PPP1R3A as a central regulator makes sense because the gene plays a critical role in the metabolism of glucose within cells, Ashley said.

What's more, the same networks that pointed researchers to PPP1R3A also turned up dozens of other new gene interactions during heart failure.

Ashley and colleagues confirmed PPP1R3A's causal role in heart failure by testing the effect of the gene — or lack thereof — in mouse models of high blood pressure. It turned out that mice lacking the PPP1R3A gene maintained normal heart function, whereas those with the gene succumbed to heart failure.

"Across the population, there are plenty of people with high blood pressure who never go into heart failure, and there are some that do," Ashley said. "We're sort of mimicking that in these mouse studies. If we were able to inhibit this gene somehow in humans, we could potentially have a therapeutic drug that could protect patients from heart failure."

Other Stanford authors of the paper include graduate students Elizabeth Chin and Michael Gloudemans; former postdoctoral scholar Ayca Erbilgin, PhD; lab manager Ching Shang; research scientists Yong Huang, MD, and Kevin Smith, PhD; former Stanford instructor of medicine and of microbiology and immunology Alex Chang, PhD; former Stanford fellow Frederick Dewey, MD; research associate Kathia Zaleta, PhD; former research scientist Daryl Waggott; study coordinator Aleksandra Pavlovic; life science research assistant Mingming Zhao, MD; professor of pediatrics Daniel Bernstein, MD; associate professor of pathology Stephen Montgomery, PhD; and assistant professor of medicine Matthew Wheeler, MD.

Researchers from the University of Pennsylvania, Boston University, the Cleveland Clinic, Providence Medical Group, the University of Maryland, the University of California-San Francisco, The Children's Hospital of Philadelphia, UCLA and Indiana University also contributed to the study.

Ashley is a member of Stanford Bio-X, the Stanford Cardiovascular Institute and the Stanford Maternal & Child Health Research Institute.

This study was funded by the National Institutes of Health and the National Science Foundation.

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

# Finding in mice points to potential treatment for vestibular disorders

**By Mandy Erickson**

Researchers at the School of Medicine have found a way to regenerate hair cells in the inner ears of mice, allowing the animals to recover vestibular function. It's the first time such recovery has been observed in mature mammals.

If further research shows that the technique can be applied to humans, it would be an initial step toward treating vestibular disorders, such as dizziness. There is currently no effective treatment for dizziness and balance disorders caused by damaged or lost vestibular hair cells. The only available therapy is teaching patients coping mechanisms through physical therapy.

> "This disabling condition is very common among the elderly, and one of the primary causes of falls."

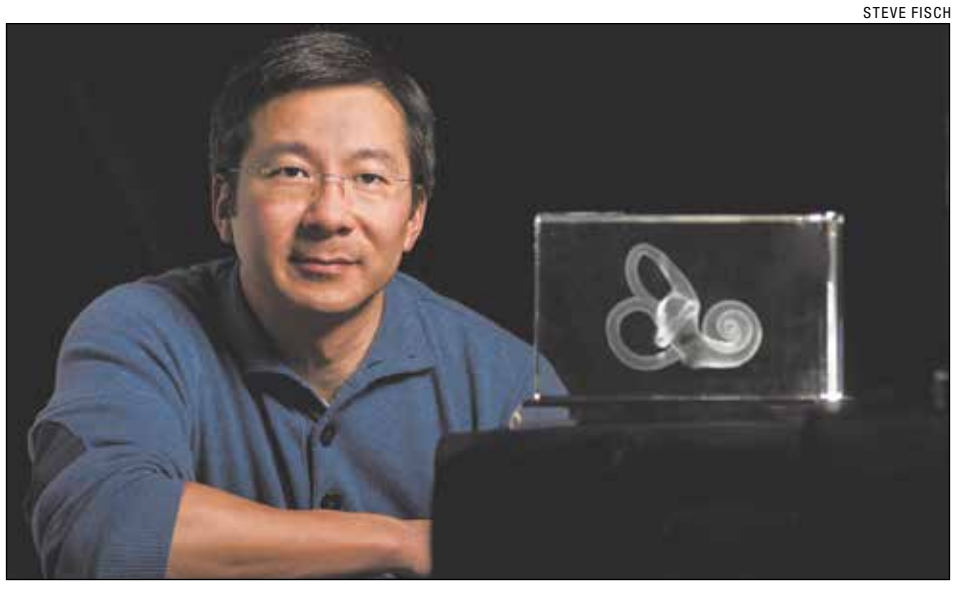
"This disabling condition is very common among the elderly, and one of the primary causes of falls," said Alan Cheng, MD, associate professor of otolaryngology-head and neck surgery.

Cheng is the senior author of a paper about the research, which was published July 9 in *Cell Reports*. Zahra Sayyid, an MD-PhD student at Stanford, is the lead author.

The hair cells in the utricle, a section of the inner ear, help maintain balance and spatial orientation and regulate eye movement. Some antibiotics can damage these cells. Damage can also occur from infections or genetic disorders, or as a result of aging. In mature mammals, vestibular hair cells regenerate on their own only minimally. (Birds and fish, however, have the ability to completely regenerate them.)

In the United States, about 69 million people experience vestibular dysfunction, some because of problems with inner ear hair cells. They can feel as if they're spinning, lose their balance easily, suffer from nausea and have **See EAR, page 5**

STEVE FISCH



Alan Cheng and his collaborators were able to regenerate hair cells inside the ears of mice.

# Immune cells invade aging brains, disrupt nerve cell formation, study finds

**By Bruce Goldman**

A study by School of Medicine investigators has revealed that immune cells infiltrate the rare newborn nerve-cell nurseries of the aging brain. There's every reason to think those interlopers are up to no good. Experiments in a dish and in living animals indicate they're secreting a substance that chokes off new nerve cell production.

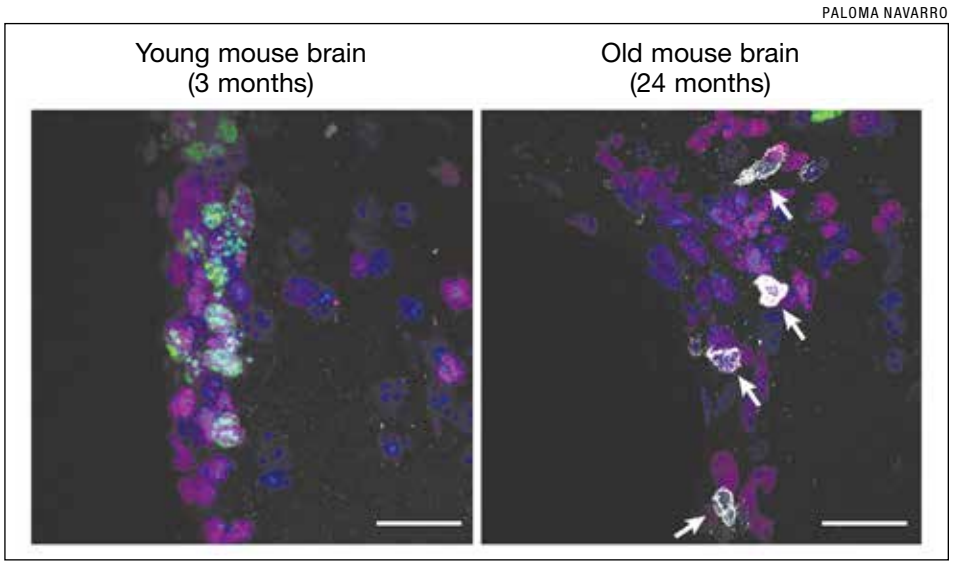
While most of the experiments in the study were carried out in mice, the central finding — the invasion, by immune cells called killer T cells, of neurogenic niches (specialized spots in the brain where new nerve cells, or neurons, are generated) — was corroborated in tissue excised from autopsied human brains.

The findings could accelerate progress in hunting down the molecules in the body that promote the common deterioration of brain function in older individuals and in finding treatments that might stall or even reverse that deterioration. They also signify a crack in the wall of dogma that's deemed the healthy brain impervious to invasion by the body's immune cells, whose unbridled access to the organ could cause damage.

"The textbooks say that immune cells can't easily get into the healthy brain, and that's largely true," said Anne Brunet, PhD, professor of genetics and senior author of the study. "But we've shown that not only do they get into otherwise healthy aging brains — including human brains — but they reach the very part of the brain where new neurons arise."

Lead authorship of the study, published online July 3 in *Nature*, is shared by medical student Ben Dulken, PhD, graduate student Matthew Buckley and postdoctoral scholar Paloma Navarro Negredo, PhD.

PALOMA NAVARRO




T cells (white) are absent, and neural stem cells (purple) much more prone to proliferate (green), in younger mice's subventricular zone (left panel) than in those of older mice (right panel.)

### The cells that aid memory

Many a spot in a young mammal's brain is bursting with brand new neurons. But for the most part, those neurons have to last a lifetime. Older mammals' brains retain only a couple of neurogenic niches, consisting of several cell types whose mix is critical for supporting neural stem cells that can both differentiate into neurons and generate more of themselves. New neurons spawned in these niches are considered essential to forming new memories and to learning, as well as to odor discrimination.

In order to learn more about the composition of the neurogenic niche, the Stanford researchers catalogued, one cell at a time, the activation levels of the genes in each of nearly 15,000 cells extracted from the subventricular zone (a neurogenic niche found in mice and human brains) of healthy 3-month-old mice and healthy 28- or 29-month-old mice.

This high-resolution, single-cell analysis allowed the scientists to characterize each cell they looked at and see what activities it was engaged in. Their analysis confirmed the presence of nine familiar cell types known to compose the neurogenic niche. But when Brunet and her colleagues compared their observations in the brains of young mice (equivalent in human years to young adults) with what they saw in the brains of old mice (equivalent to people in their 80s), they identified a couple of cell types in the older mice not typically expected to be there — and barely present in the young mice. In particular, they found immune cells known as killer T cells lurking in the older mice's subventricular zone.

The healthy brain is by no means devoid of immune cells. In fact, it boasts its own unique version of them, called microglia. But a much greater variety of immune cells abounding in the blood, spleen, gut and elsewhere in the body are ordinarily denied entry to the brain, as the blood vessels pervading the brain have tightly sealed walls. The resulting so-called blood-brain barrier renders a healthy brain safe from the intrusion of potentially harmful immune cells on an inflammatory tear as the result of a systemic illness or injury.

"We did find an extremely sparse population of killer T cells in the subventricular zone of young mice," said Brunet, who is the Michele and Timothy Barakett Endowed Professor. "But in the older mice, their numbers were expanded by 16-fold."

That dovetailed with reduced numbers of proliferation-enabled neural stem cells in the older mice's subventricular zone. Further experiments demonstrated several aspects of the killer T cells' not-so-mellow interaction with neural stem cells. For one thing, tests in laboratory dishware and in living animals indicated that killer T cells isolated from old mice's subventricular zone were far more disposed than those from the same mice's blood to pump out an inflammation-promoting substance that stopped neural stem cells from generating new nerve cells.

Second, killer T cells were seen nestled next to neural stem cells in old mice's subventricular zones and in tissue taken from the corresponding neurogenic niche in autopsied brains of old humans; where this was the case, the neural stem cells were less geared up to proliferate.

### Possible brain-based antigens

A third finding was especially intriguing. Killer T cells' job is to roam through the body probing the surfaces of cells for biochemical signs of a pathogen's presence or of the possibility that a cell is becoming, or already is, cancerous. Such telltale biochemical features are called antigens. The tens of billions of killer T cells in a human body are able to recognize a gigantic range of antigens by means of receptors on their own surfaces. That's because every unexposed, or naïve, killer T cell has its own unique receptor shape.

When an initially naïve killer T cell is exposed to an unfamiliar antigen that fits its uniquely shaped receptor, it reacts by undergoing multiple successive rounds of replication, culminating in a large set of war-like cells all sharing the same receptor and all poised to destroy any cells bearing the offending antigen. This process is called clonal expansion.

**Finding immune cells known as killer T cells lurking in older mice's subventricular zones.**

The killer T cells found in old mice's brains had undergone clonal expansion, indicating likely exposure to triggering antigens. But the receptors on those killer T cells differed from the ones found in the old mice's blood, suggesting that the brain-localized killer T cells hadn't just traipsed through a disrupted blood-brain barrier via passive diffusion but were, rather, reacting to different, possibly brain-based, antigens.

Brunet's group is now trying to determine what those antigens are. "They may bear some responsibility for the disruption of new neuron production in the aging brain's neurogenic niches," she said.

Brunet is a member of Stanford Bio-X, the Stanford Cancer Institute, the Stanford Cardiovascular Institute and the Wu Tsai Neurosciences Institute at Stanford.

Other Stanford study co-authors are basic life research scientist Naresha Saligrama, PhD, DVM; neuropathology fellow Romain Cayrol, MD, PhD; former postdoctoral scholars Dena Leeman, PhD, and Katja Hebestreit, PhD; MD-PhD students Benson George and John Pluvinage; Tony Wyss-Coray, PhD, professor of neurology and neurological sciences; Irving Weissman, MD, professor of pathology and of developmental biology and director of the Stanford Institute for Stem Cell Biology; Hannes Vogel, MD, professor of pathology and of pediatrics; and Mark Davis, PhD, professor of microbiology and immunology and director of the Stanford Institute for Immunity, Transplantation and Infection.

The work was funded by the National Institutes of Health, Tim and Michele Barakett, the National Science Foundation, the Stanford Medical Scientist Training Program and the Human Frontiers Science Program.

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

GREGG SEGAL

Anne Brunet is the senior author of a study that found intrusive immune cells in a part of the brains of older humans and mice where nerve cells are born. The intruders appear to impair nerve cell generation.

## Ear

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trouble tracking objects with their eyes. The symptoms can prevent patients from engaging in activities, including exercise and driving, and can lead to social isolation.

To study these vestibular disorders, the researchers impaired the inner ear hair cells of mice and measured how well they regenerated on their own. The researchers found that about a third of the cells regenerated spontaneously but appeared immature, and vestibular function was inconsistent.

Next, they manipulated Atoh1, a transcription factor that regulates hair cell formation, in the mice. In the animals that overexpressed Atoh1, as much as 70% of hair cells regenerated. The regenerated cells appeared relatively mature, and about 70% of these mice recovered vestibular function.

"This is very exciting. It's an important first step to find treatment for vestibular disorders," Cheng said. "We couldn't get sufficient regeneration to recover function before."

The researchers plan to study how other methods to enhance Atoh1's function may affect regeneration.

While the finding is a proof of concept, "it has opened the door for many more possibilities that could lead to treatment in people with vestibular disorders," Sayyid said.

Other Stanford co-authors of the study are research scientist Tian Wang, MD, PhD, and medical student Leon Chen.

Researchers at the University of Nebraska also contributed to the study.

The work was funded by the National Institutes of Health, the Stanford Medical Scholars Research Program, the Howard Hughes Medical Institute, the Stanford Medical Scientist Training Program, the Lucile Packard Foundation for Children's Health, the Stanford Maternal & Child Health Research Institute, the Nebraska Tobacco Settlement Biomedical Research Development Fund, the Department of Defense, the Akiko Yamazaki and Jerry Yang Faculty Scholar Fund and the California Institute for Regenerative Medicine.

Stanford's Department of Otolaryngology-Head and Neck Surgery also supported the work. ISM

5 QUESTIONS

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

# On RNA's role in diagnosing rare diseases

*An individual's genetic makeup, or genome, can reveal important and intimate details of his or her biology. Now, scientists are showing that RNA, the lesser-known molecular cousin of DNA, is powerful in its own right and can provide insights into rare human diseases that DNA cannot. Stephen Montgomery, PhD, associate professor of pathology and of genetics at the School of Medicine, is among the scientists harnessing RNA to identify the cause of rare diseases that have eluded mainstream medicine.*

*In a study published June 3 in* Nature Medicine*, Montgomery and his colleagues describe how RNA sequencing, or transcriptomics, helps pin down the genetic roots of rare diseases. While DNA sequencing of the genome can reveal certain mutations or gene abnormalities present from birth, RNA transcriptomes show what happens when those genes are turned on, or expressed, as well as how our environment can sway the activation and level of expression of our genes.*

*Science writer Hanae Armitage spoke with Montgomery about his work in transcriptomics, its role in disease diagnosis and some of the rare diseases he and his team were able to identify using insights from RNA.*

### 1 What is transcriptomics?

**MONTGOMERY:** We're probably all aware that DNA makes up all of our genes. But for these genes to actually have an effect, their genetic code is used to make molecules that are useful in the body, such as a proteins. During this process, there's an intermediate step where the DNA of a gene is expressed, and it gets transformed into molecules known as messenger RNA. This mRNA clues us into which genes are active in an individual. Collected as a whole, these mRNA molecules form the transcriptome. It allows us to study the activity of all the genes in a particular cell, or in a particular biological state. We can, for instance, use a sample of an individual's blood to determine which genes are active at any given time, like when he or she is experiencing a strange medical symptom. But unlike DNA, which is more like a static blueprint of a person's biology, mRNA is dynamic. Depending on what people do — smoke, eat fatty foods, run, whatever — it can change how genes are expressed, and we can use those expression patterns to decipher all sorts of different health risks or exposures.

Stephen Montgomery

### 2 How do you use transcriptomics to zero in on the cause of difficult-to-diagnose diseases?

**MONTGOMERY:** Right now with genome sequencing we can identify hiccups in the DNA, such as mutations, which are more broadly known as gene variants. But we all have a variety of these gene variants, and not all of them are bad; some don't have any effect. With transcriptome sequencing, we're able to see if those genes, variants and all, are functioning normally. Sometimes a gene that looks fine on the level of its DNA is actually malfunctioning, producing too much or too little protein, for instance. And we can detect this from the transcriptome.

So when evaluating a patient's transcriptome, the two things that we've focused on have been the level of gene expression and how that level compares to levels in healthy individuals, as well as something called splicing, which is how the transcript — the raw sequence of RNA after transcription — is pieced together to make the correct sequence of mRNA.

### 3 Can you give me an example of a case where transcriptomics helped identify the cause of a rare disease?

**MONTGOMERY:** We had a female who was experiencing problems with normal development. After developing normally until she was 18 months, she started having problems with head control and speech; at 21 months, she started developing tremors; and at 22 months, seizures. So we did DNA sequencing and we found about 110 different genes that could have been causing the problem. But by adding information from her transcriptome, we were ultimately able to home in on one specific gene because we saw a particular abnormality in the mRNA. The abnormality we found reflected knowledge from the literature about aberrant mRNA patterns that can lead to symptoms similar to hers. So using the transcriptome allowed us to narrow down a very large number of candidate genes to one, which gave us some real traction on this case. Our hope is that in the future, we'll be able to use this information in developing new approaches for gene therapy as that field continues to advance.

### 4 How often do rare disease diagnoses benefit from transcriptome data?

**MONTGOMERY:** With genome sequencing, we can find promising gene candidates for people who come in with an undiagnosed rare disease 30% to 50% of the time. After that, there's a diagnostic maze of different things that an individual might have to undergo to figure out what's happening. There might be an environmental factor at play that's impacting their illness. Or perhaps there are multiple genes involved in their disease. These individuals are faced with finding the next step of disease interpretation. So in this study, we asked, "If we used transcriptome sequencing and applied it across a really broad range of disorders, how many people could we help find a diagnosis or more specific information about what's causing their disorder?" We found that for an additional 8 percent of patients, we could find the cause of their illness, and for another 17 percent, we were able to narrow down the candidate genes to understand what's behind their disease. So overall, it's about a quarter of the cases that we're getting improved traction on, in terms of getting closer to a diagnosis. We think this is only the lower bound on what is possible.

### 5 How do you see this approach fitting into health care?

**MONTGOMERY:** Scientists in this field are really trying to think about how we can create and use technologies that have the broadest possible human impact and are not just for a select few individuals. It's true that some sequencing technology is still very expensive, but we've seen dramatic drops in the cost of genome sequencing over the last 20 years, particularly in the last decade. And to get individual transcriptomes sequenced now is on the order of a couple hundred dollars. My expectation is that these approaches will continue to get cheaper and more accessible, especially as researchers and doctors continue to demonstrate the value and utility of these approaches in the clinic.

In addition, I think the public will become more accustomed to not only understanding their genome and DNA variants, but also to the fact that there's valuable information in the functional outputs of their genome — such as mRNA and proteins. This can provide really detailed information about the environments they're living in, the aging process, how they might react to certain drugs, all sorts of things that we just don't have good tests for right now. I think in the future, people will get their transcript sequenced multiple times throughout their life, just as they might have their blood cell counts measured at a clinical visit. I don't think it's too far of a stretch to imagine that, down the line, doctors will be able to access transcriptome profiles of their patients more routinely to better inform care. **ISM**

## Cancer

**continued from page 1**

is diagnosed, clinicians like Alizadeh, Diehn and Kurtz assess the initial symptoms, the cell type from which the cancer originated and the size and location of the tumor after the first imaging scan to generate an initial prognosis. More recently, clinicians have also been able to assess the amount of tumor DNA circulating in a patient's blood after the first one or two rounds of therapy to determine how the tumor is responding and estimate a patient's overall risk of succumbing to their disease.

But each of these situations gives a risk based on a snapshot in time rather than aggregating all the data available to generate a single, dynamic risk assessment that can be updated throughout the course of a patient's treatment.

"What we're doing now is somewhat like trying to predict the outcome of a basketball game by tuning in at halftime to check the score, or by watching only the tipoff," Diehn said, "when in reality we know that there are any number of things that could have happened during the first half that we aren't taking into account. We wanted to learn if it's best to look at the latest information available about a patient, the earliest information we gathered, or whether it's best to aggregate all of this data over many time points."

Alizadeh and his colleagues gathered data on more than 2,500 DLBCL patients from 11 previously published studies for whom the three most common predictors of prognosis were available. They used the data to train a computer algorithm to recognize patterns and combinations likely to affect whether a patient lived for at least 24 months after seemingly successful treatment without experiencing a recurrence of their disease. They also included information from 132 patients for whom data about circulating tumor DNA levels were available prior to and after the first and second rounds of treatment.

"Our standard methods of predicting prognoses in these patients are not that accurate," Kurtz said. "Using standard baseline variables, it becomes almost a crystal ball exercise. If a perfectly accurate test has a score of 1, and a test that assigns patients randomly to one of two groups has a score of 0.5 — essentially a coin toss — our current methods score at about 0.6. But CIRI's score was around 0.8. Not perfect, but markedly better than we've done in the past."

### Identifying better treatment options

The researchers next tested CIRI's performance on data from previously published panels of people with a common leukemia and another on breast cancer patients. Although the prognostic indicators varied for each disease, they found that, by serially integrating the predictive information over time, CIRI outperformed the standard methods. Furthermore, it suggested that it might be useful to identify patients who might need more aggressive intervention within one or two rounds of treatment rather than waiting to see if the disease recurs.

"What I didn't expect was that aggregating all this information through time may also be predictive," Alizadeh said. "It might tell us 'you're going down the wrong path with this therapy, and this other therapy might be better.' Now we have a mathematical model that might help us identify subsets of patients who are unlikely to do well with standard treatments."

The researchers are next planning to test CIRI's predictive capabilities in people recently diagnosed with aggressive lymphoma.

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

Other Stanford authors of the study are visiting medical student researcher Joanne Soo; medical student Michael Jin; research scientist Chih Long Liu, PhD; assistant professor of biomedical data science Aaron Newman, PhD; and professor of biomedical data science and of statistics Robert Tibshirani, PhD.

Authors from University Hospital Essen, the Hospital F. Mitterrand, the University of Texas MD Anderson Cancer Center, the University of Schleswig-Holstein, the University Hospital Rostock, Laboratory Medical Immunology Erasmus MC, the National Cancer Institute, the University of Eastern Piedmont, the Oncology Institute of Southern Switzerland and Institute of Oncology Research, and the University of Cologne also contributed to the study.

The research was supported by the National Institutes of Health, the Damon Runyon Cancer Research Foundation, the American Society of Hematology, the Leukemia and Lymphoma Society, the V Foundation for Cancer Research, the Conquer Cancer Foundation of the American Society of Clinical Oncology, the Emerson Collective Cancer Research Fund, a Stinehart/Reed Award, the Shanahan Family Fund and the Ludwig Institute for Cancer Research.

Alizadeh is a member of the Stanford Child Health Research Institute, the Stanford Institute for Stem Cell Biology and Regenerative Medicine, the Stanford Cancer Institute and Stanford Bio-X.

Alizadeh, Diehn and Newman are cofounders of Palo Alto-based CiberMed Inc., a biomarker discovery company.

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

# Stroke

continued from page 1

had been disrupted for 45 minutes with a procedure that causes a stroke.

### Leading cause of disability

Strokes are the fifth-leading cause of death and the leading cause of disability in the United States because the accompanying brain injury is hard to undo or work around.

"It's a huge problem," Andreasson said. "The best treatments available now, clot-busting drug infusions and clot-removing surgery, are useful only for a fraction of those who experience strokes — and in many cases only if these interventions are done within the first several hours afterward. But the deleterious immune activity we've focused on in this study is typical and goes on for days."

The great majority of strokes occur because a clot lodges in a blood vessel supplying the brain with oxygen and other nutrients. The sudden oxygen cutoff damages the brain tissue dependent on that blood vessel. Once circulation resumes, inflammation-generating breakdown products of dead or dying cells are carried off from the injured brain to distant sites in the body, drawing the attention of immune "first responders" called myeloid cells that reside mainly in the spleen — effectively a barracks for immune cells — and bloodstream. The brain junk jams many of those myeloid cells into inflammatory gear, inducing them to migrate to the brain in search of trouble.

The blood vessels pervading the brain have tightly sealed walls that normally bar myeloid cells' entry into the organ. But those cells can penetrate this so-called blood-brain barrier if it's been compromised by the breakdown of blood vessel walls where a stroke has occurred. Inflammation in the brain persists for several days after a stroke, further damaging tissue and compounding patients' loss of function.

Many myeloid cells, but not other immune cells, express detectable amounts of a protein known as TREM1 on their surfaces. TREM1, Andreasson said, is an "inflammatory loudspeaker" that, when activated, drives myeloid cells into a frenzy. While TREM1 presumably serves the legitimate function of spurring myeloid cells to attack pathogens, TREM1 overdrive has been implicated in sepsis, atherosclerosis, cancer and other diseases.

### Halting friendly fire

There are no available therapies for halting myeloid cells' friendly fire on brain tissue after a stroke. But Andreasson and her colleagues were able to do so in mice by blocking TREM1.

Andreasson and her colleagues first showed that TREM1 levels in myeloid cells in the spleen and bloodstream spiked soon after mice experienced strokes. Within 48 hours of the stroke, substantial numbers of TREM1-rich myeloid cells had reached the stroke-affected part of the brain. Their numbers began to decline only two days later, and they were still present at day six — suggesting that defusing these cells even as late as several days after a stroke could be beneficial.

When the scientists compared the effects of a stroke on regular mice with other mice in which the gene for TREM1 had been deleted, they found that mice missing the gene had smaller affected brain areas and higher survival rates, moved faster, walked better, reared up on their hind legs better and were steadier on their feet.

The Stanford researchers reproduced the effects of deleting TREM1 by systemically injecting regular mice with a decoy peptide called LP17. This protein segment, effectively a small slice of TREM1, soaks up substances that ordinarily bind to and fire up TREM1. Mice given LP17 just as blood flow to the brain resumed after the stroke-inducing procedure were protected from consequences of the disease. Markedly fewer myeloid cells made their way to the brain, yielding stroke-affected brain areas less than half the size of those in animals given placebo injections. Beneficial effects were also seen if LP17 was given at 4.5 hours after the stroke. Serial LP17 injections at 4.5, 18, 26 and 48 hours after a stroke significantly raised mice's motor coordination and other measures of neurological soundness one week after the stroke.

"Giving the animals LP17 was almost as good as deleting TREM1," Andreasson said.

The researchers learned, to their surprise, that during the post-stroke inflammatory melee, gut-dwelling myeloid cells pile on. Trillions of often helpful and usually harmless bacteria occupy the intestinal lumen, the hollow core of the intestine. When a stroke hits, the sympathetic nervous system, which innervates the intestine, delivers a jolt rendering the ordinarily tightly sealed gut wall leaky. Bacteria can exit the lumen and, for the first time, encounter the standing army of macrophages — a major myeloid cell type — parked in the intestinal lining.

TREM1 expression on gut macrophages jumped after a stroke, unleashing inflammation that further loosened the gut wall, the scientists found. But administering LP17 at the start of a stroke reduced gut permeability and consequent bacterial leakage into the bloodstream.

LP17 is being tested in clinical trials in France for countering sepsis, a life-threatening storm of systemic inflammation caused when the immune system overreacts to a microbial infection.

"If this decoy peptide winds up working in sepsis, it's a no-brainer to try it in stroke," Andreasson said.

Andreasson is a member of the Wu Tsai Neurosciences Institute at Stanford, Stanford Bio-X and the Stanford Cardiovascular Institute. **ISM**

# Dawes

continued from page 1

was able to keep everybody happy and moving forward until we reached the point where we were too successful and didn't have enough room."

Dawes also advocated for children at the national level, playing an active role in creating guidelines for coverage of children under the Affordable Care Act. He retired from the hospital in 2018.

Paul King took over as CEO of Lucile Packard Children's Hospital-Stanford Children's Health in January. "Chris never lost track of why we're here, and why we do what we do. He understood at a fundamental level the profound difference that we could make in the lives of children and families when we come together in teams to share better ideas and better practices — that when applied consistently create the magic and miracle of healing," King said.

Lloyd Minor, MD, dean of the Stanford School of Medicine, said Dawes will be remembered for his enormous contributions to maternal and child health. "Chris was a tireless advocate for children's health. Through his passion and dedication, he helped bring extraordinary advances in clinical services to our young patients," Minor said. "An exceptional colleague and leader, he will be greatly missed by the entire Stanford Medicine community."

David Entwistle, president and CEO of Stanford Health Care, worked together with Dawes and Minor to create the Stanford Medicine integrated strategic plan. "It was wonderful to partner with an outstanding leader like Chris as our two hospitals and the medical school worked in concert to determine our collective future direction and how best to get there. We found tremendous success in our ability to work together and collaborate," Entwistle said.

"Beyond his effective leadership, what I will remember most about Chris are his kindness and dedication to the mission of helping children in need," said Stanford President Marc Tessier-Lavigne, PhD. "He leaves behind a significant legacy at the Lucile Packard Children's Hospital Stanford, having taken the institution to a new level. He truly created the children's hospital of the future."

### British native

A native of Great Britain, Dawes came to California with his family as a child. Though he had early dreams of being a commercial airline pilot, he eventually found his way into hospital administration. He attended San Diego State University, where he obtained a bachelor's degree in public administration in 1974, and went on to earn an MBA from the McLaren School of Business at the University of San Francisco in 1984.

For more than 10 years, he worked in senior administrative positions at Pacific Presbyterian Medical Center in San Francisco, Santa Clara Valley Medical Center in San Jose and Stanford Health Care. He joined Packard Children's as its chief operating officer in 1995.

Shortly after that, the children's hospital became part of a merger between Stanford Health Care and UC-San Francisco. Dawes oversaw the successful integration of the pediatric programs at the two leading academic medical centers. Though the merger ultimately failed, he distinguished himself as a strong leader during the process and became the CEO of Lucile Packard Children's Hospital in 1997.

"I wasn't sure about becoming a CEO, in part because there's a lot of politics, a lot of diplomacy and I was more interested in day-to-day operations," Dawes said in a 2017 interview with the Silicon Valley Business Journal. "I learned fairly quickly that as a CEO, you're not there to problem-solve. You are there to help coach and guide people so that they will make the right decisions. My job is to provide the vision, hire good people, set the direction and let them do the problem-solving."In consulting with the medical staff, Dawes realized that if the hospital were to be truly great, it would have to build up its specialty programs and recruit the best talent available. He oversaw a $500 million campaign, one of the largest ever for a U.S. children's hospital, and helped attract more than 100 top faculty in their fields to lead new programs in heart and cancer care, brain and behavior, transplantation, pulmonary disease, and pregnancy and newborn care.

Dawes also came to recognize the importance of research to Packard's academic mission and became a strong supporter of an initiative now known as the Stanford Maternal and Child Health Research Institute. Over the course of a decade, the institute has provided more than $52 million to Stanford investigators in both the clinical and basic sciences.

Harvey Cohen, MD, PhD, former chief of pediatrics at the hospital, said Dawes succeeded in part because he had an excellent rapport with members of the medical staff and was responsive to their ideas and needs. "He listened to us and understood what it would take to build clinical and academic programs," said Cohen, the Deborah E. Addicott-John A. Kriewall and Elizabeth A. Haehl Family Professor in Pediatrics. "That was the attribute that allowed him to lead us from being a reasonably good regional children's hospital to one of the best children's hospitals in the country."

### Expanding the hospital

As the hospital's national reputation grew, it began to attract more patients and to outgrow its space. Under Dawes' direction, hospital officials launched a massive undertaking to expand on neighboring land, doubling the hospital's size to 521,000 square feet and adding six operating rooms and 149 beds. The new, 361-bed hospital features extensive artwork, 3½ acres of gardens and many family-friendly features. It opened to patients in December 2017.

Dawes also oversaw the creation of a regional health care network to enable patients and families to readily access Packard's services throughout the Bay Area and the West Coast. The network, known as Stanford Children's Health, now has 60 locations in Northern California and is the only health system in the area — and one of the few in the country —exclusively dedicated to pediatric and obstetric care.

"The goal was to make it accessible to everyone within 10 miles of their home. That was Chris' vision — that Packard should be part of everybody's family," said David Stevenson, MD, the Harold K. Faber Professor of Pediatrics and senior associate dean of maternal and child health at the School of Medicine.

The idea of embracing family was very much in keeping with Dawes' character. "He was very approachable and warm," Stevenson said. "He focused on you. He listened to you. He had a fatherly disposition that was very welcoming and supportive. His hardest problem was saying no. He always wanted to be helpful and responsive."

Dawes was also involved in children's organizations at the national and state level. He was the former chair of the board of trustees for the National Association of Children's Hospitals and Related Institutes and for the Child Health Corporation of America; both are now part of the Children's Hospital Association. During the development of the Affordable Care Act, he spent much time in Washington, D.C., helping ensure that children would be appropriately covered.

He served on the board of directors for the Solutions for Patient Safety Project, a network of more than 80 children's hospitals in the United States working to create a safe and healing environment for children. He also was a board member of the California Hospital Association, the California Children's Hospital Association and the Silicon Valley Leadership Group.

When asked in a 2018 interview what he saw as his legacy, he said, "I am very proud of the work we do for children and pregnant women. Collectively we have created an organization that is admired nationally, and is a place that attracts great faculty and staff. We have a terrific future."

Though his professional accomplishments were many, Dawes was proudest of his family. He is survived by his wife, Elizabeth (Beth) Dawes of Los Altos; son Scott Dawes of San Jose and daughter-in-law Brittney Dawes, and son Matthew Dawes of San Francisco; daughter Sara Dawes Hughes and son-in-law Caleb Hughes of Spokane, Washington; and two great-nephews, Antonio and David Gonzalez.

Arrangements for a celebration of his life are pending. In lieu of flowers, the family requests donations made in Dawes' honor be directed to the Lucile Packard Foundation for Children's Health. **ISM**

# New Stanford Hospital gets temporary certificate of occupancy

After more than a decade of planning, design and construction, the new 824,000-square-foot Stanford Hospital reached a major milestone on July 5, receiving a temporary certificate of occupancy. This clears the way for Stanford Health Care to begin staffing and stocking the new hospital while minor, final work on it is completed.

This milestone marks the final leg of construction on the new Stanford Hospital before it opens for patient care in the fall.

"Our new hospital will be a place for firsts. New discoveries will be made here. New procedures will be performed. And through this remarkable state-of-the-art facility, we will be able to revolutionize the way that patient care is delivered at Stanford," said David Entwistle, president and CEO of Stanford Health Care. "It's wonderful to see our vision for the future of patient care coming to life, and I am grateful to our exceptional team who helped us reach this point."

Once completed, the new facility will accommodate the latest advances in medical technology; increase capacity; revolutionize the treatment of rare, complex diseases; meet new seismic safety requirements; and transform the way patient care is delivered in the community.

"More than 5.5 million construction work hours have been completed on the hospital from 135 trades and specialties to date," said Bert Hurlbut, vice president of construction for the new hospital. "This milestone triggers many transitions, the most noticeable being that hard hats and safety gear will no longer be needed in most areas of the building."

While minor finishing work continues, Stanford Health Care will begin the extensive operational training and preparation necessary to license a new hospital facility where Stanford Medicine's lifesaving treatment and care will occur.

"It's quite an extraordinary process to bring a new hospital like this online," said Helen Wilmot, vice president of facilities services and planning. "More than 4,000 physicians, nurses, staff and volunteers will undergo rigorous training this summer to familiarize themselves with the new hospital before it opens to patient care this fall."

Designed by the internationally recognized firm Rafael Viñoly Architects, the new Stanford Hospital sets a global standard for patient care. The new hospital blends a human-centered approach to care with a razor-sharp focus on integrating technological advancements into every aspect of medical care delivery. Four acres of gardens, original art and sweeping views share the spotlight with state-of-the-art interventional operating and imaging suites, digitally driven patient rooms and access to a premier team of specialists from across Stanford Medicine.

"Through the new Stanford Hospital, we are taking an important step forward in realizing our vision of precision health: to predict, prevent, and cure disease — precisely," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "In every aspect of its design, our new facility enables us to provide high-tech, high-touch care to our patients and bring the latest biomedical advances to the bedside."

The community will be invited to tour the building as part of its community open house on Sept. 14 and 15. More information about the opening events is available at www.stanfordhealthcares.com. ISM

DARIUS RILEY

Hard hats and other safety gear are no longer required in most areas of the new Stanford Hospital, which will open in the fall.

## OF NOTE

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

Cristina Alvira

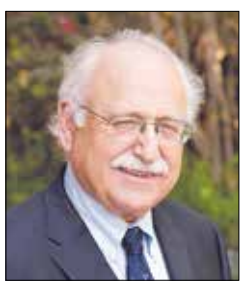
Charles K. F. Chan

Nida Degesys

Karen Hirsch

Gabriel Mannis

Greer Murphy Jr.



Alan Schatzberg

Manali Patel

Thomas Quertermous

Laura Roberts

Kavita Sarin

Birgitt Schuele

Edda Spiekerkoetter

Pervez Sultan

**CRISTINA ALVIRA**, MD, was appointed associate professor of pediatrics, effective March 1. Her research aims to identify mechanisms that direct lung growth and repair in infants and children, with the goal of developing new treatments for pediatric lung diseases.

**CHARLES K.F. CHAN**, MD, assistant professor of plastic and reconstructive surgery, has been awarded an arthritis and aging research grant, sponsored by the American Federation for Aging Research and the Arthritis National Research Foundation. The $100,000 grant will fund his research to identify a way to resurface osteoarthritic joints with new cartilage.

**NIDA DEGESYS**, MD, clinical instructor in emergency medicine, was named fellow of the year by the Emergency Medicine Residents' Association. The $500 award recognizes a member who has demonstrated significant dedication to promoting the goals and objectives of the association at local, state and national levels, and who has a record of creativity, enthusiasm and accomplishment in addressing emergency medicine issues.

**KAREN HIRSCH**, MD, was promoted to associate professor of neurology and neurological sciences, effective March 1. Her clinical focus is on caring for critically ill patients with neurologic disorders, including traumatic brain injury, stroke and post-cardiac arrest coma. Her research examines techniques for targeting resuscitation and predicting outcomes in patients with cardiac arrest and traumatic brain injury.

**GABRIEL MANNIS**, MD, was appointed assistant professor of medicine, effective April 1. His research focuses on developing therapies for acute leukemia, with a particular interest in using immunotherapy, targeted agents and predictive biomarkers as a means to improve outcomes and quality of life for patients with hematologic malignancies.

**GREER MURPHY JR.**, MD, PhD, professor emeritus of psychiatry and behavioral sciences, and **ALAN SCHATZBERG**, MD, the Kenneth T. Norris Jr. Professor of Psychiatry and Behavioral Sciences, have received the David A. Mrazek Award in Psychiatric Pharmacogenomics from the American Psychiatric Association. They were among the first to apply genetic technology to predict medication response in psychiatric patients and have published a series of pioneering studies, including research that identifies genetic markers that affect responses to antidepressants.

**MANALI PATEL**, MD, assistant professor of medicine, received a 2019 Research Grant on Disparities in Lung Cancer from the Lung Cancer Research Foundation with support from the Stavros Niarchos Foundation. The grant provides $150,000 over two years to support her project on using social support to engage patients in their care and improve access to end-of-life cancer care for low-income and minority patients with advanced stages of cancer.

**THOMAS QUERTERMOUS**, MD, the William G. Irwin Professor in Cardiovascular Medicine, received a three-year Seed Networks project grant from the Chan Zuckerberg Initiative. As a member of one of 38 collaborative teams funded by this grant, his work will support the continued development of the Human Cell Atlas, an international effort to map all cells in the human body. His team will work to create an atlas of single cell transcriptomic and epigenomic features of the human vasculature to define the cellular composition and key regulatory features of these vessels.

**LAURA ROBERTS**, MD, professor and chair of psychiatry and behavioral sciences and the Katharine Dexter McCormick and Stanley McCormick Memorial Professor, has been selected as the next editor-in-chief of *Academic Medicine*. Her five-year term begins Jan. 1. She is the first psychiatrist and second female editor-in-chief since the journal was founded in 1926. She served as editor-in-chief for the journal *Academic Psychiatry* from 2002-2019 and has been a member of the editorial board for *Academic Medicine* since 2013.

**KAVITA SARIN**, MD, PhD, assistant professor of dermatology, was named a Damon Runyon Clinical Investigator by the Damon Runyon Cancer Research Foundation. The three-year, $600,000 early investigator award will support her research looking at a group of patients with extreme proliferation of basal-cell skin cancer to identify the genetic mechanisms that contribute to cancer susceptibility, and to develop new nonsurgical therapies for these patients. The foundation also repays medical school debt up to $100,000 still owed by the awardee.

**BIRGITT SCHUELE**, MD, Dr. Med., was appointed associate professor (research) of pathology, effective Feb. 1. Her research uses genetics and human stem cell models to investigate the underlying causes of neurodegeneration and to develop innovative biomarkers and new therapeutic approaches for Parkinson's disease.

**EDDA SPIEKERKOETTER,** MD, was appointed associate professor of medicine, effective March 1. Her research focuses on the genetic basis of pulmonary hypertension symptoms, with the goal of identifying new treatment methods. She also investigates the development of malformations in the lung in hereditary hemorrhagic telangiectasia and co-directs the HHT clinic

**PERVEZ SULTAN**, MBChB, MD(Res), was appointed associate professor of anesthesiology, perioperative and pain medicine, effective April 1. He specializes in obstetric anesthesiology, and his research explores women's immune function and recovery following childbirth. ISM