Chronic fatigue syndrome biomarker found

By Hanae Armitage

People suffering from a debilitating and often dismissed disease known as chronic fatigue syndrome may soon have something they’ve been seeking for decades: scientific proof of their ailment.

Researchers at the School of Medicine have created a blood test that can flag the disease, which currently lacks a standard, reliable diagnostic test.

“Too often, this disease is categorized as imaginary,” said Ron Davis, PhD, professor of biochemistry and of genetics. When individuals with chronic fatigue syndrome seek help from a doctor, they may undergo a series of tests that check liver, kidney and heart function, as well as blood and immune cell counts, Davis said. “All these different tests would normally guide the doctor toward one illness or another, but for chronic fatigue syndrome patients, the results all come back normal,” he said.

The problem, he said, is that they’re not looking deep enough. Now, Davis; Rahim Esfandyarpour, PhD, a former Stanford research associate; and their colleagues have devised a blood-based test that successfully identified participants in a study with chronic fatigue syndrome. The test, which is still in a pilot phase, is based on how a person’s immune cells respond to stress.

With blood samples from 40 people — 20 with chronic fatigue syndrome and 20 without — the test yielded precise results, accurately flagging all chronic fatigue syndrome patients and none of the healthy individuals. The diagnostic platform could even help identify possible drugs to treat chronic fatigue syndrome. By exposing the patients’ blood samples to drug candidates and rerunning the diagnostic test, the scientists could potentially see which drug improved the immune cells’ response. Already, the team is using the platform to screen for potential drugs they hope can help people with chronic fatigue syndrome down the line.

A paper describing the research findings was published online April 29 in the Proceedings of the National Academy of Sciences. Davis is the senior author. Esfandyarpour, who is now on the faculty of the University of California-Irvine, is the lead author.

Providing the proof

The diagnosis of chronic fatigue syndrome, when it actually is diagnosed, is based on symptoms — exhaustion, sensitivity to light and unexplained pain, among other things — and it comes only after other disease possibilities have been eliminated. It is also known as myalgic encephalomyelitis and designated by the acronym ME/CFS. It’s estimated that 2 million people in the United States have chronic fatigue syndrome, but that’s a rough guess, Davis said, and it’s likely much higher.

For Davis, the quest to find scientific evidence of the malady is personal. It comes from a desire to help his son, who has suffered from ME/CFS for about a decade. In fact, it was a biological clue that Davis first spotted in his son that led to the diagnosis of a blood test that accurately identified people with chronic fatigue syndrome.

By Erin Digitaile

Social behavior improved in children with autism after they inhaled a hormone called vasopressin, a pilot study by researchers at the School of Medicine has found. It is the first study to test transnasal vasopressin for any indication in children. Although small, the placebo-controlled study of 36 children provides early evidence that vasopressin may reduce social impairments in the developmental disorder, which affects 1 in 59 U.S. children. The findings were published online May 1 in Science Translational Medicine.

“Social deficits are one of the core features of autism and a challenging area for many kids with the disorder,” said the study’s lead author, Karen Parker, PhD, associate professor of psychiatry and behavioral sciences at Stanford. “Some of these kids want to socially connect but aren’t capable of doing so.”

The other core features of autism are poor verbal communication skills and restricted, repetitive behaviors. No existing medications address any core features of the disorder.

In the trial, parents’ and experts’ ratings of social behavior indicated more improvement in children treated with vasopressin than in those given a placebo. Vasopressin-treated children also experienced new research could pave way for flu vaccine that lasts for life

By Amy Adams

If the virus that causes flu were an ice cream cone, then the yearly vaccine teaches the immune system to recognize just the scoop — chocolate one year, strawberry the next. As the virus changes each year, so too must the vaccine.

A new approach that teaches the body to recognize the cone portion of the virus, which stays the same year to year, could shake up that yearly vaccination ritual and protect people against pandemic flu like the one that killed 40 million to 50 million people in 1918. The team working on this new approach, led by Stanford biochemist Peter Kim, PhD, has shown early signs that their technique works in lab animals. They caution, however, that they still need to make their vaccine more specific and show it works in much larger studies before testing it in people.

“We think it could be very generalizable,” said Kim, the Virginia and D.K. Ludwig Professor in Biochemistry and the lead investigator of the infectious disease initiative at the Chan Zuckerberg Biohub. “It could be important for coming up with a universal flu vaccine that would protect against pandemic flu, as well as for HIV.”

Focusing the immune system

First, a primer on flu vaccines. The idea is to inject a person with either a killed virus or just a single protein normally found on the virus surface. The immune system learns to recognize bits of that artificial invader, and mounts a defense that it can activate months or even years later if it sees that protein again. The challenge is that some portions of a protein are, for whatever reason, a lot easier for the immune system to detect. In the case of flu, that easily detected portion is the ice cream cone, thus the annual vaccine against the flavor of the year.
Reservoir bugs: Study shows why stomach pathogen tough to eradicate

By Bruce Goldman

The stomach-dwelling bacteria Helicobacter pylori survives in the stomach — a hellish, churning vat of hydrochloric acid — by holing up inside organs that pit-like glands and establishing quarterback’s rights. Once the germ has set up shop, School of Medicine investigators have learned, even competing strains of the same species can’t dislodge it, or even share its hideout.

The findings, published online May 2 in PLoS Biology, raise questions about the effectiveness of probiotic approaches, in which “good” germs are ingested in an effort to supplant “bad” germs. Yet the findings also hint at possibly effective ways to deal with the potentially life-threatening H. pylori strains now inhabiting one of every two human stomachs.

“This study changes the way we think about how microbes like H. pylori establish their chronic persistence in the body,” said Manuel Amieva, MD, PhD, associate professor of pediatrics and of microbiology and immunology, who is the study’s senior author. The lead author is former graduate student Connie Fung, PhD.

H. pylori is the primary cause of stomach ulcers and stomach cancer. Fortunately, the great majority of infected people get ulcers, and only 1% get stomach cancer.

Plus, there are reasons for thinking that infection by H. pylori, which has co-existed with humans since the earliest days of our species, may have some advantages. For instance, H. pylori infection is associated with lower incidences of asthma and other allergies. The combination of these effects and the low-incidence hypothesis suggests that H. pylori’s adverse effects give pause to medical researchers considering ways to preemptively eradicate it from all our stomachs. It may be wiser to substitute friendly “designer” strains.

But that won’t be easy, the study showed.

Succeeding where others fail

From an ecological point of view, H. pylori has succeeded where practically every other bacterial pest has failed — by developing the capacity to persist for prolonged periods — often for a person’s entire life — in the stomach, whose intense acidity, swiftly shifting chemical contents and rapid cellular turnover make it one of the harshest environments a microbe encounters.

Although H. pylori is susceptible to antibiotics, it’s not uncommon for these drugs to fail to completely clear the stomach of the microorganism. “The re-emerging strain is invariably just the same as the one through which it has been eradicated,” Amieva said, suggesting the presence of some niche where H. pylori can find refuge and replenish its numbers in safety. But exactly why the microbe would choose to hang out where it was not obvious.

In a study published in 2015, Amieva’s group discovered the presence of H. pylori within stomach glands, but why the microbe would choose to hang out there was not obvious.

The new study, Amieva said, shows that once a particularly hardy, or lucky, individual H. pylori bacterium manages to colonize a gland, the resulting “founder” strain becomes extremely difficult to dislodge even by members of an essentially identical strain, for reasons that remain mysterious but may have to do with the fact that each gland has only a single, tiny entry point.

Glowing green and red

The researchers inoculated mice’s stomachs with two versions of an otherwise identical H. pylori strain, differing only in that one group had been genetically modified so it emitted fluorescent green light when stimulated by light, while the other group was modified to glow red. Later, the scientists could observe the different-colored strains’ success in establishing themselves within glands along the length of the mice’s stomachs.

The researchers used a form of microscopy that allowed them to move their focus through successive depths of stomach tissue and trace the bugs to any individual gland, a “red” or “green” H. pylori strain sends forth individual progeny to adjacent glands in which they plant their flags, thrive, exclude newcomers, multiply and eventually release new single-celled troops to repeat the gland-by-gland expeditive advantage.

“Precisely which tools the bacteria need to establish squatting rights in a gland is still a matter of guesswork. But when the scientists inoculated mouse stomachs with mutant H. pylori lacking the functioning chemical sensor machinery that guides its swimming direction, the bugs were unable to maintain exclusive colonies in glands,” Amieva said.

This raises the issue of how to eradicate potentially pathogenic bacterial strains en- sconced in our bodies or how to replace them by others that are less pathogenic. Probiontics have not demonstrated much success in achieving that goal yet, Amieva said.

“It’s not enough to find a good probiotic strain that can survive in the gut, it must be shown to live in me,” he said.

“You need to create space for it.”

One potential approach, Amieva suggested, would be to find some way to draw the bacteria out of their protective hideouts before treating them and then re- place them with a less-virulent strain. Amieva is a member of the Stanford Maternal & Child Health Research Institute.

Other Stanford co-authors are former graduate student Shumin Tan, PhD; basic life science research associate Mifuyu Nakajima, PhD; postdoctoral scholar Jessica Klein, PhD; and Tadashi Fukami, PhD, associate professor of biology.

Researchers from the University of California-Davis and the Wellcome-Sanger Institute in England also contributed to the study.

The work was funded by the National Institutes of Health, the National Science Foundation, the Ameri- can Gastroenterology Association, a Mordudge Fellowship, the Child Health Research Institute, a Wellcome Trust grant and the Wellcome-Sanger Institute in England also contributed to the study.

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Inside Stanford Medicine is a monthly publication that features stories from all areas of Stanford Medicine, the institution that includes the Stanford HealthCare system and the Stanford University School of Medicine. The magazine is distributed to more than 500,000 households within a 50-mile radius of the Stanford campus.

New research links brain injury from low oxygen to specific cells

By Erin Digitaile

Low oxygen levels are a well-known cause of brain injury in premature babies. But the mechanism by which low oxygen hurts the developing human brain has been unclear.

Now, researchers at the School of Medicine have identified a specific set of brain cells that are particularly susceptible to harm from low oxygen exposure in early development. This damage is congruent with brain abnormalities, particularly reduction in gray matter, seen among children who are born very prematurely.

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den born before 28 weeks’ gestation, or at least 12 weeks’ early, have a thiner cerebral cor-
text than children born after a full-term pregnancy. The cerebral cortex is a folded layer of gray matter that makes up a large portion of the brain in humans and other primates. It is responsible for advanced brain functions, including cognition, language and the processing of sensory and motor information.

Neurologists have also long recog- nized that lung development is incomplete in very premature babies. The brain and lungs share a tiny entry point. And even after a full-term birth, the brain centers that control the infants’ breathing are not fully mature. These factors raise their risk for drops in blood oxygen and
**Physician burnout in the United States may have passed its high-water mark. According to a survey conducted by Taz Shaheen, MD, director of Stanford's WellMD Center, doctors were doing a little better in 2017 than in 2014. Even so, they're worse off than people in other professions. In 2017, about 44 percent of doctors reported that they experienced at least one symptom of burnout, while only about a quarter of other professionals said the same.**

Postdoctoral scholar Rachael Schwartz, PhD, and her colleagues at the School of Medicine decided to look for some solutions outside the health care field. They interviewed 50 people in non-medical jobs that require interpersonal connection — salespeople, firefighters, lawyers, educators, musicians, social workers, yoga instructors and others — to learn how different professions address professional wellness. An article about their research was published online April 29 in the Journal of General Internal Medicine.

Science writer Mandy Erickson asked Schwartz about the tactics practiced in other professions, and what the medical field could learn from them.

1. Do certain professions have good strategies for preventing burnout? How do they do it?

**SCHWARTZ:** No professions stand out, but we found a set of core behaviors and trainings in wellness that transcend professions. In many of our findings, we see Maslow’s hierarchy of needs: Professionals have time during the workday to fulfill basic self-care needs. They also need social support and opportunities for meaningful appraisals.

On the practical side, we found a number of ways that organizations can support professional wellness. Many of the people interviewed said they were grateful when their organization allowed for the scheduling flexibility necessary to attend to self-care. For some, this took the form of longer lunch breaks or time during the workday to attend to their personal needs. Across professions, we heard in a big difference to have time built into the workday for peer support. For example, a teacher explained she needed to chat with other teachers about the workday for peer support. For example, a police officer issued a teen an essay assignment instead of a citation when he was found with marijuana at school. The essay he asked her to write — about how she thought her actions would influence her future and those around her — ended up being meaningful to him as well as to the girl and her family.

In another example, a hospice volunteer was asked to read Psalms to a patient, but he didn't know any because he isn't Christian — he's Hindu — so he looked them up online. He was surprised to learn how much his religion echoed the same core tenets as his own. And a documentary filmmaker described how he likes being open to “being changed by somebody,” rather than simply seeking practical information.

When professionals approached challenges as opportunities to foster connection, they experienced more meaningful, rewarding engagements.

2. How do people manage workplace stress on an individual level?

**SCHWARTZ:** The people we interviewed used emotional distancing practices to avoid absorbing their clients' distress. A fire captain employs a mantra: “It’s not my emergency.” Interviewees also set boundaries around their work so that both their professional success and their own emotional well-being: They refer clients to other resources when the clients’ problems exceed the scope of their job. Interestingly, it wasn’t just people in what we think of as more emotionally stressful environments: Teachers, firefighters, or even a software developer who employed these tactics. They were common in all the professions.

3. What are some of the tactics people employ to find meaning in a stressful work environment?

**SCHWARTZ:** Creativity and connection appear to be key to staying mentally healthy. For example, a police officer issued a teens an essay assignment instead of a citation when she was found with marijuana at school. The essay he asked her to write — about how she thought her actions would influence her future and those around her — ended up being meaningful to him as well as to the girl and her family.

In another example, a hospice volunteer was asked to read Psalms to a patient, but he didn't know any because he isn't Christian — he's Hindu — so he looked them up online. He was surprised to learn how much his religion echoed the same core tenets as his own. And a documentary filmmaker described how he likes being open to “being changed by somebody,” rather than simply seeking practical information.

When professionals approached challenges as opportunities to foster connection, they experienced more meaningful, rewarding engagements.

4. What organizational changes are needed to improve wellness?

**SCHWARTZ:** We found that leaders’ modeling of self-care was crucial to creating a culture in which employees felt empowered to protect their own wellness. Leaders who modeled vulnerability — who acknowledged their own need for psychological help and who encouraged community participation — normalized the need for psychological processing. These leaders endorsed self-care as central to being productive effectively.

Other leaders emphasized connection between leaders and individual employees and through community participation. One firefighter said, “The leader is the emotional nexus of the organization, and the tone they set is pervasive. … There are some tasks, that for me are just a constant. But it’s choosing in a human that’s the key.”

5. What can the medical field learn from other professions?

**SCHWARTZ:** I was surprised to find that many other fields have well-developed protocols in place for protecting the emotional well-being of their staff. Practicing medicine is inherently emotionally challenging, but medical professionals are not typically provided with supports that are as robust as the infrastructure necessary to protect their own wellness. We could stand to borrow a model from the fire captain we interviewed: His organization holds critical incident debriefings in which psychiatrists and firefighters facilitate healing conversations. The meetings are routine after traumatic events, but they also occur monthly.

It helps to have leaders who acknowledge that workers will struggle with vicarious trauma and who provide a forum for emotional processing. In medicine we have models for peer support, such as Balint groups and Schwartz rounds, in which trained facilitators lead monthly meetings, but these are not yet institutionalized as central to maintaining professional wellness. Peer support appears to be essential to wellness regardless of the emotional nature of the work, but for those practicing medicine, it should be universally provided.

We need to have leaders who set the tone they set is pervasive. … There are some tasks, that for me are just a constant. But it’s choosing in a human that’s the key.”

Rachael Schwartz

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**Brain**

**continued from page 2**

**subsequent brain injury.**

Pasca and her colleagues found that many cells in the developing brain are unhurt by exposure to low oxygen. However, in the submerged progenitors within the subventricular zone, a region responsible for the growth of the human cortex, are severely affected. These are the cells that eventually give rise to mature brain cells, including neurons.

**Creating brain spheroids**

“Most of human brain development, specifically in the second and third trimesters of pregnancy, is inaccessible for direct study,” said senior author Sergiu Pasca, MD, assistant professor of psychiatry and of neuroscience at Stanford. “The discovery was possible because Sergiu and Anca Pasca — who are married to each other and run a lab at Stanford — and their colleagues previously figured out how to create three-dimensional cell cultures that mimic structural and functional aspects of the parts of the developing human brain. They call these brain spheroids or organoids.

Sergiu and Anca Pasca and their team previously published studies showing that the brain spheroids resembling the cerebral cortex develop the same general organization, including deep and superficial layers of cortex, and are acquired at roughly the same timeline.

“It is quite remarkable how these blobs of cells, if provided with the right cues, will differentiate, organize and mature in a dish,” Sergiu Pasca said.

In the new study, the team grew brain spheroids until they contained cell populations and gene-expression markers similar to human brain tissue midway through gestation. The researchers used these cortical spheroids to study gene expression at 24 and 48 hours, then re-ordered the oxygen levels. They examined changes in gene expression at 24 and 48 hours into the low-oxygen period, as well as 72 hours after oxygen levels had returned.

As expected, the scientists saw gene-expression changes after 24 and 48 hours in genes known to respond to hypoxia. They also saw changes in a group of genes expressed in the subventricular zone, an area rich in progenitor cells that generate neurons in mid- and late pregnancy. Closer analysis showed these progenitor cells were not dying. Rather, they were being differentiated into neurons sooner than normal, a change that could lead to fewer neurons in total.

A stress pathway responsive to the unfolded protein response, a stress response pathway that transitions cells from a “growth” mode to a “survival” mode.

“We were surprised, but it was a good some paper things that are important. But it’s checking the tone they set is pervasive. … There are some tasks, that for me are just a constant. But it’s choosing in a human that’s the key.”

**Testing a compound**

The researchers also tested whether a small molecule that restores aspects of the unfolded protein response could reverse the brain spheroids’ response to low oxygen. The molecule, called ISRIB, prevented the reduction in intermediate progenitors following low-oxygen exposure. “It’s exciting because our findings tell us that we could potentially use this pathway could interfere with hypoxic injury to the brain, and potentially help with preventing damage,” Sergiu Pasca said.

Other Stanford co-authors of the paper are research scientist Jin-Yong Park, PhD; visiting associate professor Hyun-Woo Shin, MD, PhD; postdoctoral scholar Omar Reval, DVM, PhD; Ruth O’Hara, PhD, professor of psychiatry and behavioral sciences; and Theo Palmer, PhD, professor of neurosurgery.

Anca and Sergiu Pasca are members of the Stanford Maternal & Child Health Research Institute, the Wu Tsai Neurosciences Institute, the National Institutes of Health, and the MQ Scholar Network. Sergiu Pasca is a fellow of Stanford ChEM-H.

Sergiu Pasca is a professor of neurosciences and a research scientist at the Stanford Neurology Institute and the University of California-San Francisco also contributed to the research.

The research was supported the National Institutes of Health, the MQ Fellow Award, the New York Stem Cell Foundation, the Kwan Rebreuker Fellowship, the Wu Tsai Neurosciences Institute, the National Institutes of Health, the MQ Scholar Network, the National Institutes of Health, the MQ Scholar Network, the University of California-San Francisco also contributed to the research.

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Synthetic biology used to target cancer cells and spare healthy tissue

By Krista Conger

Synthetic proteins engineered to recognize overly active biological pathways can kill cancer cells while sparing their healthy peers, according to a study by researchers at the School of Medicine.

The customizable approach, which the researchers call RASER, redirected cancerous proteins fused to two proteins: The first is activated in the presence of an “always on” growth signal often found in cancer cells, and the second carries out a researcher-programmed response, such as triggering the expression of genes involved in cell death.

Although the experiments were confined to cells grown in the laboratory, the researchers believe the results could lead to a new type of cancer therapy in which synthetic proteins deliver highly targeted and customizable treatments to side-step the sometimes devastating side effects of current options.

“We’re effectively rewiring the cancer cells to bring about an outcome of our choosing,” said Michael Lin, MD, PhD, associate professor of neurobiology and of bioengineering. “We’ve always searched for a way to kill cancer cells but not normal cells. Cancer cells arise from faulty signals that allow them to grow inappropriately, so we’ve hacked into cancer cells to redirect these faulty signals to something useful.”

A paper describing the work was published May 2 in Science. Lin is the senior author. Former graduate student Hokyung Chung, PhD, is the lead author.

Signals from receptors

Many cancers rely on a series of signals that originate from proteins called receptors that span the membrane of the cell. These signaling cascades, or pathways, are used by healthy cells to grow in response to external cues, for example during development or recovery from injury. Often, however, these receptor proteins are mutated or overexpressed in cancer cells in ways that render the receptor protein “always on,” providing the cell with constant, unwarranted signals for growth. The receptors focused on two receptors, EGFR and HER2 — members of a family of receptors called the ErbB receptors — that often drive the growth of brain, lung and breast cancers. HER2, for example, is targeted by Herceptin in breast cancer.

Many common anti-cancer drugs, including Herceptin, work by blocking the cascade of signals triggered by receptor activation. Unfortunately, however, these drugs have no way to discriminate between cancerous cells, in which the pathway is always activated, and healthy cells going about their business as usual. That’s where Lin and his team come in.

“We haven’t had a drug that can tell the difference between a pathway signaling normally and one that is abnormally active,” Lin said. “We knew we needed a better strategy, a more rational way of treating cancer. But we’ve not had a way to do it until recently.”

Designing a synthetic protein

Chung and her colleagues designed a synthetic protein consisting of two natural proteins fused together — one that binds to active ErbB receptors and another that cleaves a specific amino acid sequence — then engineered a second protein that binds to the inner surface of the cell membrane and contains a customizable “cargo” sequence that can carry our specific actions in the cells.

When the first protein binds to an active ErbB receptor, it cuts the second protein and releases the cargo into the interior of the cell.

“When the receptor protein is always on, as it is in cancer cells, the released cargo protein accumulates over time,” Chung said. “Eventually enough accumulated proteins can have an effect on the cell. In this way, the system produces an effect only in cancer cells, and we can convert the always-on state of the receptor into different outcomes through the choice of cargo protein.”

After several rounds of tinkering, the team saw that their RASER system, which stands for “rewiring of aberrant signaling to effecter release,” was highly specific for cancer cells dependent on ErbB receptor activity. For their first test they chose to use a protein involved in triggering cell death as the RASER cargo.

Killing only overactive cells

The team compared the RASER system to two therapies currently used for metastatic breast cancer — a chemotherapy regimen and a drug that blocks ErbB activity — on several types of cultured cells: breast and lung cancer cells in which the ErbB pathway was overly active; breast cancer cells in which ErbB activity was normal; and noncancerous breast and lung cells. They found that RASER was both more specific and generalizable, and it allows us for the first time to selectively target cancer cells while sparing normal signaling pathways.

Lin is a member of Stanford Bio-X and Stanford ChEM-H, as well as of the Stanford Maternal & Child Health Research Institute and the Wu Tsai Neurosciences Institute at Stanford.

The study was supported by the National Institutes of Health, a Stanford Graduate Fellowship, the Huy Foundation, the Burroughs Wellcome Foundation, a Damon Runyon-Rachelle Innovation Award and an Alliance for Cancer Gene Therapy Young Investigator Award.

Researchers work toward understanding flatworms’ regenerative powers

By Nathan Collins

Slice it into 100 pieces if you want, and the millimeter-long flatworm called a planarian won’t particularly care. Each piece can grow back into a new worm. How they do that, and what scientists could learn about how to regenerate our own bodies, has remained mysterious because one of the most valuable investigative tools — gene editing — has so far not worked in these animals. The hurdle has been getting planarian cells to take up gene editingtechnology. Now, a Stanford graduate student named Hall has found a way. The work has already delivered successful therapy in the lab, and new research suggests that it might be a step toward treatments for human health problems.

“Our work on planarian cells is a first step toward understanding the complicated mechanisms that can convert the always-on state of the receptor into different outcomes. We are confident that there’s a lot of optimization that can be done,” said Hall.

Wang is optimistic, too. “Being able to genetically manipulate the worms would be a huge step.”

RATTIX/THOMAS KIENZLE/AUTOSTOCK.COM

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May 6, 2019

Inside Stanford Medicine
Like many dedicated researchers, Sandrene Cassells, from Stanford School of Medicine, has devoted considerable time and effort to applying her expertise to medical issues. "It’s been rewarding to serve as a mentor to students with distinct research interests," Cassells said.

Cassells chose to pursue research in atrial fibrillation, a heart rhythm disorder that affects more than 2.5 million people in the U.S. alone. Her research focuses on developing personalized devices to map and treat the condition.

"We’re increasing technological advancements, and so, the romantic notion of keeping an eye on the heart during open surgery has been removed through a much smaller open-incision approach," Cassells said. "And so, ongoing is the battle is the question of how we’re increasing technology to address medical issues and keep track of medical parameters like blood pressure and blood sugar, but if we’re not tackling the social aspects, then we run the risk of leaving certain patients behind.

"Physicians have been aware for quite a while that those factors have the largest impact on health care outcomes in comparison to things like genetics or medical treatment," Cassells said. "And so, going forward, the need is to address social determinants of health — such as poverty, access to housing, food insecurity, immigration status, exposure to domestic violence — and what barriers might deter doctors from routinely doing so as part of their clinical interactions with patients."

"It’s been rewarding to serve as a mentor to students with distinct research interests," Cassells said.

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By Julie Greicius

As a child, Jon Sole wanted to know why he could remember a phone number, but his relative, who had an intellectual disability, could not. His interest in that question persisted through his undergraduate years at Johns Hopkins, where he began studying the science of memory. Now a fourth-year medical student at Stanford, Sole is exploring the brain mechanisms that underlie memory.

"It’s been rewarding to serve as a mentor to students with distinct research interests," Cassells said.

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"It’s been rewarding to serve as a mentor to students with distinct research interests," Cassells said.
Autism continued from page 1

some reductions in anxiety and repeti-
tive behaviors. We saw across multiple measures independently,” Parker said. “It is really exciting.”

“We might finally have an agent that will target these core features that are very hard to treat,” said the study’s senior author, Antonio Hardan, MD, professor of psychiatry and behavioral sciences at Stanford. The researchers are now testing vasopressin in 100 additional children with autism to see if the pilot findings can be replicated.

“Before getting too excited, I want us to replicate this, and more importantly I want others to replicate our findings,” added Hardan, who is also director of the Autism and Developmental Disabilities Clinic at Lucile Packard Children’s Hospital at Stanford. Large-scale studies also needed to assure the drug’s safety. Sex-specific social hormones

Vasopressin is a tiny protein hor-
mine, nine amino acids long, manufac-
tured in the hypothalamus. It differs by two amino acids from oxytocin, another hormone made in the same part of the brain.

Although both hormones play roles in social behavior, there are sex differences in their activity. Parker’s early research in animal models showed that, in male, vasopressin influences pair-bonding and fatherng behavior. Oxytocin regulates maternal behaviors and social bonding in females.

Parker and Hardan have previously shown that, compared with typically developing children, those with autism have lower vasopressin levels in their cerebrospinal fluid, which bathes the brain and spinal cord. Among children with autism, those with the lowest CSF vasopressin levels also have the lowest social functioning, the researchers have proved by the Food and Drug Administration or will they can test their finding in a clinical trial in the future. CFS still respond poorly to stress and generate a spike again,” Esfandyarpour said.

Assessing autism symptoms

At the beginning and end of the trial, several measurements were used to assess autism symptoms. Participants’ parents completed questionnaires rating their children’s social abilities. In the lab, the researchers tested participants’ ability to recognize emotional states in images of people’s eyes or facial expressions. Chil-
dren’s repetitive behaviors and anxiety levels were also measured. The research-
ers also completed physical and chemical

In addition, among children with the highest vasopressin at baseline, vasopres-
sin treatment reduced restricted and re-
petitive behaviors. This finding did not occur in participants with lower base-
line vasopressin.

The findings will guide larger trials of vasopressin. ‘Identifying who responds and why it is really important,’” Parker said. Because autism exists on a spectrum, with some people more severely affected than others, treatments must be individ-
ualized, she said.

If the findings of the pilot trial are replicated, it would be an important step toward validating the safety of the hormone in large populations and to understand which aspects of social behavior are most improved by vasopressin,” Esfandyarpour added. ‘Is it motivation, affiliation, attachment? Ability to understand others’ mental states or read facial expressions or body language?’ he said. ‘This has opened up a lot of possibilities for individuals with autism.”

Other Stanford co-authors of the study are research scientist Ozge Ozkan, PhD; clinical research coordinator Robin Libove; former life sciences researcher Noreen Molusi; research scientist Debra Karlson, PhD; former assistant clinical research coordinator Raena Sumiyoshi; incoming medical resident Jacqueline Summers; Kyle Himmel, MD, clinical assistant professor of psychiatry and be-

lished as an article in Science Translational Medicine. In a larger cohort of participants.

Doubling up

In addition to diagnosing ME/CFS, the research-
ers are also harnessing the platform to screen for drug- based treatments, since currently the options are slim. Using the nanoelectronics assay, we can add controlled doses of many different potentially therapeutic drugs to the patient’s blood samples and run the diagnostic test again,” Esfandyarpour said.

If the blood samples taken from those with ME/ CF just respond poorly to stress and generate a spike in electrical current, then the drug likely didn’t work. However, a drug seems to mitigate the jump in electrical activity, which means it is helping the immune cells and plasma better process stress. So far, the team has already found a candidate drug that seems to restore healthy function to immune cells and plasma when tested in the assay. The drug, while successful in the assay, is not currently being used in people with ME/ CF, but Davis and Esfandyarpour are hopeful that they can test their finding in a clinical trial in the future.

All of the drugs being tested are either already ap-
proved by the Food and Drug Administration or will soon be broadly accessible. Davis said. “It’s a good idea to fast access and dissemination should any of these com-
pounds pan out.”

Other Stanford authors of the study are research sci-
entists Mohsen Nemat-Gorgani, PhD, and Julie Wil-
helmy; and research assistant, Alex Kashi.

The study was funded by the Medicine Foun-
dation. Davis is the director of the foundation’s scien-
tific advisory board.

Stanford’s departments of Genetics and of Biochem-
istry also supported the work.

Memorial service for Oscar Salvatierra set for May 23

The Stanford community is invited to at-tend a memorial service for Oscar Salvatierra, MD, professor emeritus of surgery and of pe-

diatrics at the School of Medicine, to be held from 6:7-30 p.m. May 23 at the Arrillaga Alumni Center.

Salvatierra, who founded the pediatric kid-
ney transplant program at Lucile Packard Chil-dren’s Hospital Stanford, was a leader in the effort to enact national legislation regulating organ donation. He died March 16. He was 85.

LUCILE PACKARD FOUNDATION FOR CHILDREN’S HEALTH
**OBITUARY**

Roy Maffly, professor and advocate for minority students, dies at 91

By Mander Erickson

Roy Maffly, MD, former associate dean for student affairs at the Stanford University School of Medicine and a champion for underrepresented minorities to the school, died April 15 at his home in Palo Alto after a brief illness.

Maffly was rememered most for his teaching and mentoring of medical students and residents. In 1982, he was the first to latch this highly specific monoclonal antibody onto the flu virus protein in the lab and use it as a stencil.

Using that mostly cloaked protein as a vaccine may push the immune system to mount an attack against the cone — the portion of the virus shared across flu strains, including pandemic flu.

\[ \text{Flu continued from page 1} \]

though they might, scientists haven't been able to effectively direct the immune system's attention to the cone. The idea for the new approach came about when Payton Weidenbacher, a graduate student in chemistry, attended a lab presentation where scientists discussed a protein that can bind to exactly the spot on the flu virus protein they want the immune system to recognize. (The protein is called a monoclonal antibody; “mono” because it binds to just one spot, and “clonal” because scientists can make a lot of identical copies of it.) The scientists wondered if they could use the monoclonal antibody as a model and create a way for the immune system to bind to the same spot. In a twist on the discussion, Weidenbacher remembered a chemical trick that he thought might be a different approach. Instead of just learning from the monoclonal antibody, why not make use of it? His idea was to latch this highly specific monoclonal antibody onto the flu virus protein in the lab and use it as a stencil. He could paint the rest of the protein with molecules that act as a chemical cloak, rendering it invisible to the immune system. Removing the stencil would leave only a tiny portion of the protein visible for the immune system to learn to recognize and eventually attack.

\[ \text{Protein also showed an immune response to other strains of the flu — something that would only happen if their immune systems had learned to recognize the cone. Animals that received a normal vaccine didn't respond well to other flu strains.} \]

\[ \text{Kim and Weidenbacher said they "skewed" the immune response, but they have work to do to get it to be more specific. If they succeed, they said it could become an approach that works for many different infectious agents.} \]

\[ \text{"You should be able to do this on anything — that's the dream," Weidenbacher said. "With the right chemistry, you could take any monoclonal antibody off the shelf and do this."} \]

Kim is a member of Stanford ChEM-H, Stanford Institute for Stem Cell Biology and Regenerative Medicine, the Stanford Medical & Child Health Research Institute and the Wu Tsai Neurosciences Institute at Stanford.

This work was supported by the Virginia and D. K. Ludwig Fund for Cancer Research and the Chan Zuckerman Biohub.

Stanford's departments of Biochemistry and of Chemistry also supported the work. 

Peter Kim

Payton Weidenbacher

Maffly was born Nov. 26, 1927, in Berkeley, California, the son of a family with a long history in health care. His great-grandfather, Leroy Francis Herrick, also a Berkeley native, moved to San Francisco in 1952. He met his future wife, Marilyn Miles, when she was a nursing student at UCSF, and the couple married in 1952.

His research, which involved toad bladders and the passage of sodium and potassium through cell walls, informed the treatment of heart and kidney diseases.

In addition to the Gores award, Maffly won the school's Award for Outstanding Teaching in 1971; the Kaiser Award for Excellence in Teaching in 1970, 1972 and 1977; and the Arthur L. Bloomfield Award for Excellence in the Teaching of Clinical Medicine in 1977.

Rex Jensen, MD, professor emeritus of medicine, was a medical student when he first met Maffly and the two were working in a laboratory at Massachusetts General. At Stanford in 1971, the two co-founded the Division of Nephrology. At the time, nephrology was an emerging specialty.

“Students just flocked to him,” Jamison said. “He was very kind, a truly remarkable human being. I don’t think he and I ever had an argument about anything.”

After his retirement, Maffly studied history and music, a lifelong love, at Foothill College. Maffly-Kipp said he played instruments: “He was always curious and loved to learn things,” she said.

The family is planning a memorial service.

In addition to Maffly-Kipp, he is survived by his wife, Marilyn Maffly; daughter Nancy Maffly of Davis, California; son-in-law Peter Maffly-Kipp; and grandsons Wesley, Joseph and David Maffly-Kipp. His son, Robert Maffly, died in 1983.

Karla Kirkegaard

Mark Krasnow

William Weis

profition in 1983 to advise the nation on issues related to science and technology. Scholars are elected in recognition of their outstanding contributions to research. This year’s election brings the total of active academy members to 2,347.
Robert Tibshirani

Tad and Dianne Taube have committed $6 million for pediatric cancer research

By Jodi Mouratis

Silicon Valley philanthropists Tad and Dianne Taube have committed $6 million to the School of Medicine to establish the Taube Initiative in Pediatric Cancer Research, which will further the development of innovative therapies to improve the cure rates for childhood cancers.

“Tad and Dianne Taube are accelerating the development of childhood cancer therapies that are more personalized, more precise and more effective,” said Lloyd Minor, MD, dean of the School of Medicine. “I am immensely grateful for their support of Stanford Medicine’s researchers and their dedication to improving the lives of children around the world.”

The Taube Distinguished Scholar in Pediatric Immunotherapy will focus on developing and advancing immunotherapy treatments for childhood cancers. This type of therapy is associated with fewer long-term toxicities than chemotherapy and radiation, which kill cancer cells but also destroy healthy cells and weaken the immune system. Immunotherapy equips the patient’s own immune cells to specifically attack cancer cells.

The Taube Distinguished Scholar for Pediatric Oncology will focus on developing customized therapies to treat childhood cancers utilizing knowledge of the genetic differences found in cancer cells.

In addition, the initiative will support the Taube Innovation Fund in Pediatric Cancer, which will back innovative research and clinical projects within the Division of Hematology/Oncology in the Department of Pediatrics at the School of Medicine.

Stanford has built world-class clinical, research and manufacturing facilities and recruited top researchers who are leaders in translating the lessons of immunotherapy, pioneered for leukemia, into new treatments to combat intractable solid tumors that affect children.

The Taubes’ gift will help sustain this progress and continue to grow a vibrant research community committed to curing children with cancer.

“We are committed to advancing the treatment of childhood cancer, but we could not do this work without the generous support of donors like the Taubes,” said Mary Leonard, MD, professor of pediatrics and of medicine, who holds the Arline and Pete Harman Professorship for the Chair of the Department of Pediatrics. “We are very grateful for philanthropists in our community who support our efforts to help children live longer, healthier lives.”

The Taubes have given to other areas of the School of Medicine and Packard Children’s. Their recent gifts, totaling over $40 million, include:

• $9.5 million to establish the Tad and Dianne Taube Pediatric Brain Tumor Center

By Jodi Mouratis

Tad and Dianne Taube have made recent gifts totaling more than $40 million to the School of Medicine and Packard Children’s Hospital.

New Stanford Hospital nearing completion

The finish line is in sight for the new Stanford Hospital, following six years of construction. Crews are painting walls, hanging artwork, installing medical equipment and putting in furniture. This summer, hospital staff will begin training in the new space before its opening later this year.

The seven-story, 824,000-square-foot facility will accommodate advances in medical technology, increase capacity and meet new earthquake safety standards.

It will feature:

• An enlarged emergency department with twice the floor space of the current one.

• 368 individual patient rooms that provide increased privacy and comfort for patients and their families.

• 20 operating rooms, eight interventional/radiology rooms, three MRI scanners, three CT scanners and one interventional MRI scanner.

• Five gardens for patients and visitors, walking trails and a meditation room.

• A parking structure with 900 spaces.

The new building — which will be connected to the existing hospital by a second-floor pedestrian bridge, an underground tunnel and a street-level pedestrian path — is part of the Stanford University Medical Center Renewal Project. The project includes the recent expansion of Lucile Packard Children’s Hospital Stanford, a renovation of the Hoover Pavilion and new labs at the School of Medicine.

Besides all the physical enhancements, hospital teams are working on digital tools that will improve the patient experience. Patients will be able to use a new version of the MyHealth app to speed up the admitting process, get reminders about appointments and view step-by-step walking directions from the parking garage to various locations within the building.

By Jodi Mouratis

Tad and Dianne Taube

• $3 million to support a collaboration between the School of Medicine and the Gladstone Institutes focused on research related to Huntington’s disease.

• $1.4 million for the Taube Pediatric Neurodegenerative Disease Research Fund.

• $1 million to support transdisciplinary research through the Stanford Maternal & Child Health Research Institute.

By Jodi Mouratis

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