INSIDE STANFORD MEDICINE

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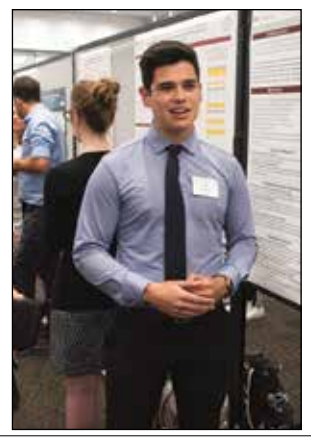


Medical students presented a broad array of projects at this year's Medical Student Research Symposium.

Page 5

Chronic fatigue syndrome biomarker found

By Hanae Armitage

People suffering from a debilitating and often discounted 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 participants' blood samples to drug candidates and rerunning the diagnostic test, the scientists could potentially see whether the 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.

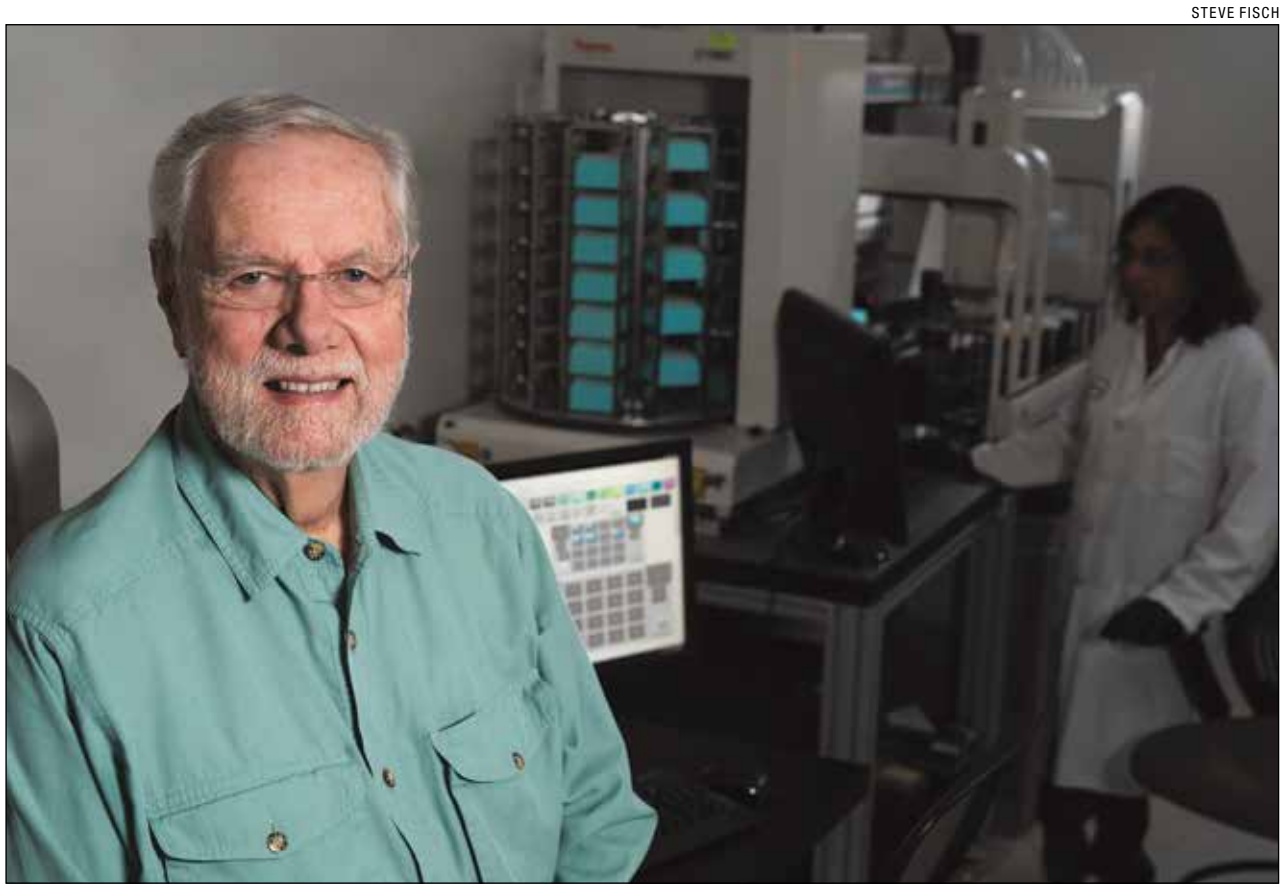
A paper describing the research findings was published online April 29 in the *Proceedings of the National Academy of Sciences*. Davis is the senior author. Esfandyarpour, who is now on the faculty of the University of California-Irvine, is the lead author.

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 See BIOMARKER, Page 6

STEVE FISCH



Ron Davis is the senior author of a paper describing a blood test that accurately idenfied people with chronic fatigue syndrome.

Hormone reduces social impairment in children with autism, study shows

By Erin Digitale

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 intranasal vasopressin for any indication in children.

Although small, the placebo-controlled study of 30 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 See AUTISM, page 6

ZOUZOU/SHUTTERSTOCK.COM

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."

IMAGE POINT FR/SHUTTERSTOCK.COM

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 end, thus the annual vaccine against the flavor of the year. Try See FLU, page 7

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 that organ's pit-like glands and establishing squatter's rights. Once the germ has set up shop, School of Medicine investigators have learned, even competing strains of the same species can't displace 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.

Manuel Amieva

"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 remain asymptomatic throughout their lives: Only 10-15% 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 that upside and the low-incidence, high-impact nature of H. pylori's adverse effects gives pause to medical researchers considering ways of preemptively eradicating it from all of our stomachs. It may be wiser to substitute friendlier "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. It has evolved 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 thought to have been eradicated," Amieva said, suggesting the presence of some niche where H. pylori can find refuge and replenish its numbers in safety. But exactly how has been unclear.

H. pylori is a corkscrew-shaped microbe equipped with a tuft of spinning, hairlike projections called flagella that enable it to swim freely in an aqueous liquid medium or to bore into viscous fluids. Microbiologists have long thought it avoids being dissolved in a sea of stomach acid by hiding out in the mucus layer that lines the stomach and protects the digestive organ from being eaten by the acid it produces.

That's part of the story. But the new study reveals a safer survival tactic for the bug: steering itself into one of the myriad pit-like glands that dot the stomach's inner surface and, afterward, fending off all comers.

> "This study changes the way we think about how microbes like H. pylori establish their chronic persistence in the body."

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 a laser, 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 scientists used a form of microscopy that allowed them to move their focus through successive depths of intact tissue rather than view separate thin tissue slices. They also used a technique called CLARITY that renders tissues transparent without destroying their microanatomical integrity. That combination let them visualize, in three dimensions, H. pylori's presence along the depths of the stomach glands.

Instead of mixing randomly — as one would expect if occupancy of a gland by one "color" of bugs presented no barrier to entry by the other color — the two sets of H. pylori occupied distinct patches of stomach-surface area, indicating an exclusive "first-come, first-served" advantage for a given gland's initial occupant and further suggesting that, having established itself within a 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 expeditionary advance.

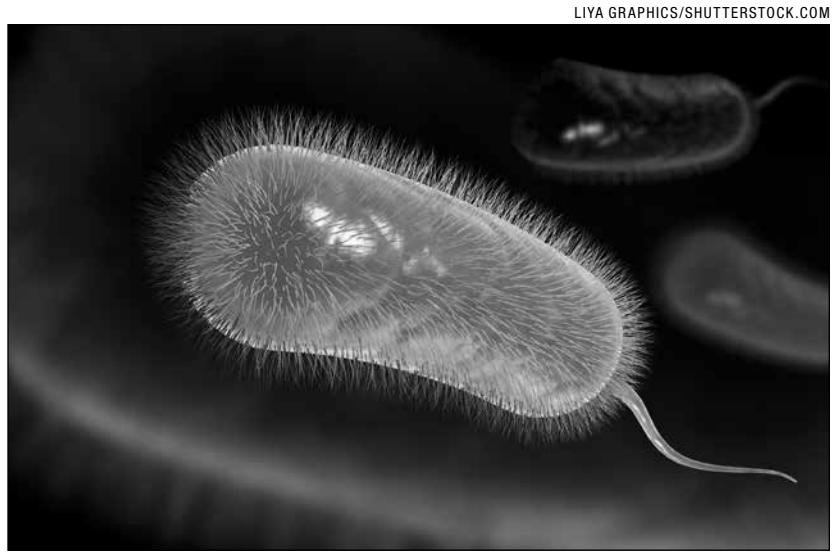
Precisely which tools the bacteria need to establish squatter's rights in a gland are still guesswork. But when the scientists inoculated mouse stomachs with mutant H. pylori lacking the functioning chemical sensor machinery that guides its swimming direction, the bugs were unable to maintain exclusive colonies in glands.

This raises the issue of how to eradicate potentially pathogenic bacterial strains ensconced in our bodies or how to replace them by others that are less pathogenic. Probiotics 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 organ you want it to live in," 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 replace them with a less-virulent strain.

LIYA GRAPHICS/SHUTTERSTOCK.COM



An illustration of H. pylori bacteria, the primary cause of stomach ulcers and stomach cancer. A new study shows how the bacteria take up residence in stomach glands.

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 American Gastroenterology Association, a Morgridge Faculty Scholar Award and the Wellcome Trust.

Stanford's departments of Pediatrics and of Microbiology and Immunology also supported the work. **ISM**

New research links brain injury from low oxygen to specific cells

By Erin Digitale

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. The researchers have also identified a compound that may be able to prevent the problem. The findings were published online today in *Nature Medicine*.

Sergiu Pasca

Anca Pasca

"In the past 20 years, we've made a lot of progress in keeping extremely premature babies alive, but 70% to 80% of them have poor neurodevelopmental outcomes," said the study's lead author, Anca Pasca, MD, assistant professor of pediatrics at the School of Medicine and a neonatologist at Lucile Packard Children's Hospital Stanford. Hypoxic brain injuries are thought to lead to neurological and psychiatric disease in some preemies, she said.

Prior research has shown that children born before 28 weeks' gestation, or at least 12 weeks early, have a thinner cerebral cortex than children born after a full-term pregnancy. The cerebral cortex is the highly 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, speech and the processing of sensory and motor information.

Neonatologists have also long recognized that lung development is incomplete in very premature babies. The babies have poor lung function, and the brain centers that control the infants' breathing are not fully mature. These factors raise their risk for drops in blood oxygen and

See BRAIN, 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

Looking for solutions to physician burnout

Physician burnout in the United States may have passed its high-water mark. According to a survey conducted by Tait Shanafelt, 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 surveyed indicated they experienced at least one symptom of burnout, while only about a quarter of other professionals said the same.

Postdoctoral scholar Rachel Schwartz, PhD, and her colleagues at the School of Medicine decided to look for some solutions outside the health care field. They interviewed 30 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 universal underpinnings to wellness that transcend professions. In many ways, our findings follow Maslow's hierarchy of needs: Professionals must have time during the workday to fulfill basic self-care needs. They also need social support and opportunities for meaningful engagement.

Rachel Schwartz

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 workdays in exchange for three-day weekends that supported rest and creativity; for others, such as a trial lawyer, this meant having the space to attend to their own needs following stressful events. Across professions, we heard it made 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 what happened in the classroom in order to not bring her work stresses home, while a police officer and firefighter shared how important it was for them to process the day's events with colleagues in order to maintain their own psychological wellness.

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 said setting boundaries was essential to both their professional success and their own emotional wellness: 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 — law enforcement, firefighting and trial law — 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 teenager 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 her 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 fulfilling professional duties effectively.

Other leaders emphasized connection between leaders and individual employees and through community-building exercises. As a school principal explained, "The leader is the emotional nexus of the organization, and the tone they set is pervasive. … There are some tasks, some paper things that are important. But it's checking in on 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 emotional training or the community support 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 institutionally endorsed 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 support infrastructure in place to protect the well-being of those who care for others. ISM

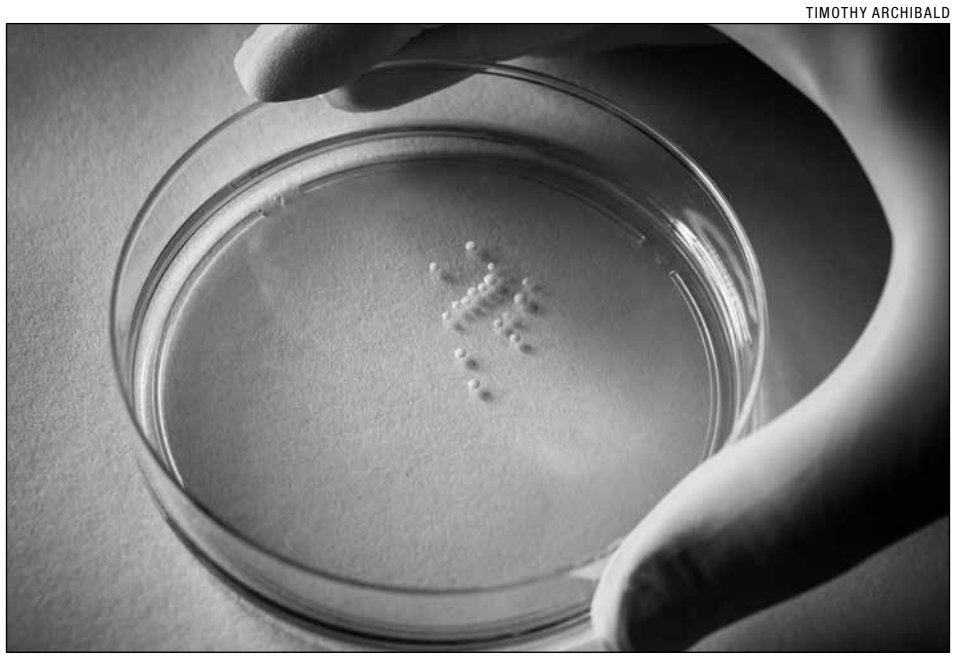
Brain

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, the intermediate progenitor cells of the subventricular zone, a region responsible the growth of the human cortex, are severely affected. These are cells that eventually give rise to mature brain cells, including neurons.

TIMOTHY ARCHIBALD



Cortical spheroids suspended in a lab dish. Researchers used such cultures to determine that low oxygen levels during brain development may cause particular cells to differentiate too soon.

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 behavioral sciences.

The discovery was possible because Sergiu and Anca Pasca — who are married to each other and each 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 have 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 on approximately 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.

A compound may be able to prevent the problem.

The researchers exposed these cortical spheroids to low oxygen for 48 hours, then restored 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 differentiating into neurons sooner than normal, a change that could lead to fewer neurons in total in the mature brain. The pathway responsible, called the unfolded protein response, is a stress-response pathway that transitions cells from a "growth" mode to a "survival" mode.

"We were surprised, but it was a good surprise," Anca Pasca said. "Looking back, it made sense."

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 pharmacologically manipulating 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-Young Park, PhD; visiting associate professor Huyn-Woo Shin, MD, PhD; postdoctoral scholar Omer Revah, DVM, PhD; Ruth O'Hara, PhD, professor of psychiatry and behavioral sciences; and Theo Palmer, PhD, professor of neurosurgery.

Anca Pasca and Sergiu Pasca are members of the Stanford Maternal & Child Health Research Institute, the Wu Tsai Neurosciences Institute at Stanford and Stanford Bio-X. Sergiu Pasca is a fellow of Stanford ChEM-H.

Scientists from Seoul National University and the University of California-San Francisco also contributed to the research.

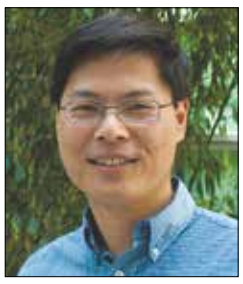
The research was supported the National Institutes of Health, the MQ Fellow Award, the New York Stem Cell Foundation, the Wu Tsai Neurosciences Institute, Stanford Bio-X, the Kwan Research Fund, the California Institute for Regenerative Medicine, the UCSF Weill Institute for Neurosciences, the Association of Medical School Pediatric Department Chairs and the Stanford Maternal & Child Health Research Institute.

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

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.



Michael Lin

The customizable approach, which the researchers call RASER, relies on just 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 sidestep 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 researchers 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.

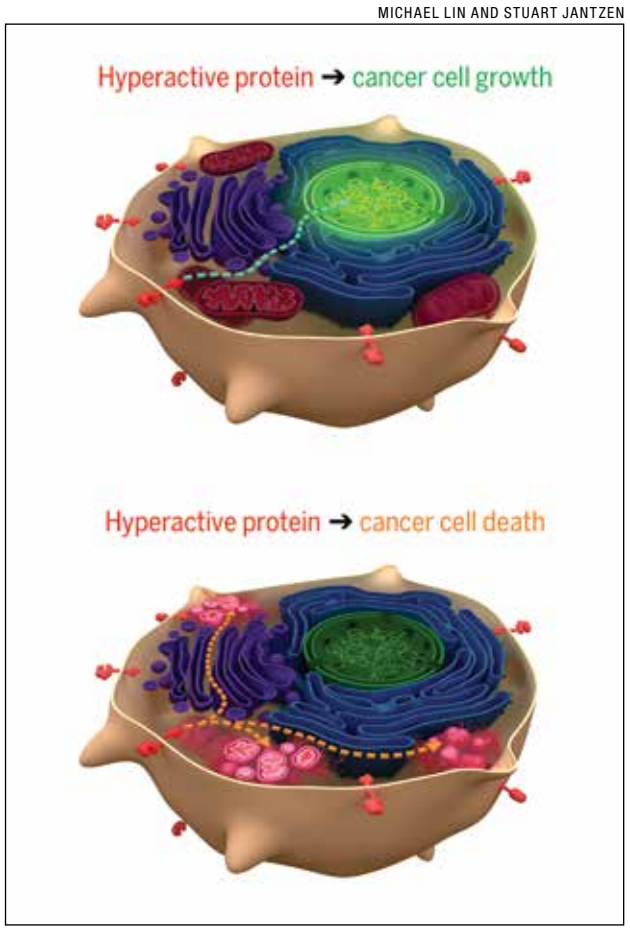
"We haven't had a drug that can tell the difference between a pathway signaling normally and one that is abnormally active," Lin said. "We knew we needed a better strategy, a more rational way of treating cancer. But we've not had a way to do it until recently."

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. They then engineered a second protein that binds to the inner surface of the cell membrane and contains a customizable "cargo" sequence that can carry out specific actions in the cell. 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 accumulates to 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."

MICHAEL LIN AND STUART JANTZEN



(Top) Some types of cancers are caused by mutated or overexpressed cell surface proteins that signal to the nucleus (green pathway) to drive uncontrolled growth and survival. (Bottom) Using an approach called RASER, the cancer-causing signals are redirected away from cell growth and survival and toward programmed cell death (orange pathway).

After several rounds of tinkering, the team saw that their RASER system, which stands for "rewiring of aberrant signaling to effector 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 cell lines.

The researchers found that the traditional chemotherapy regimen of carboplatin and paclitaxel killed all the cells indiscriminately. The effect of the ErbB pathway inhibitor on the viability of the cells varied and did not reliably correlate with ErbB pathway activity levels. Only RASER specifically killed those cells in which the ErbB pathway was overly active while sparing those in which ErbB activity was normal.

While much work remains to be done to learn whether RASER is effective in human tumors, the researchers are excited about the possibilities of re-engineering the system to recognize other receptors mutated in cancers and swapping the cargos to achieve different outcomes. Challenges include learning how best to deliver synthetic proteins into tumors and understanding how the immune system might react to RASER. But Lin is optimistic.

"We have so much more information now about cancer genomics, signaling and how cancer cells interact with the immune system," Lin said. "It's finally becoming practical to combine this knowledge with synthetic biology approaches to tackle some of these pressing human health problems. RASER is both customizable and generalizable, and it allows us for the first time to selectively target cancer cells while sparing normal signaling pathways."

Other Stanford authors of the study are graduate student Xinzhi Zou; former undergraduate student Bryce Bajar; postdoctoral scholar Veronica Brand, PhD; research scientist Yunwen Huo, PhD; Javier Alcudia, PhD, director of Stanford's Neuroscience Gene Vector and Virus Core; and James Ferrell, MD, PhD, professor of chemical and systems biology and of biochemistry.

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 Ilju Foundation, the Burroughs Wellcome Foundation, a Damon Runyon-Rachleff Innovation award and an Alliance for Cancer Gene Therapy Young Investigator Award. **ISM**

Researchers work toward understanding flatworms' regenerative powers

By Nathan Collins

Slice it into 100 pieces if you want, and the millimeters-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 new genes. As a possible solution, Stanford graduate student Nelson Hall has turned to nanoscale glass-like straws developed in the lab of engineer Nicholas Melosh, PhD, to deliver genetic material to the flatworms. It seems to be working.

> **"Being able to genetically manipulate the worms would be a huge step."**

The fact that Hall's goal now seems within reach is already an accomplishment, said Bo Wang, PhD, assistant professor of bioengineering and one of Hall's advisers. "I told Nelson it wouldn't work," he said.

With a Stanford Bio-X seed grant, Hall and his collaborators are working to optimize the technique. If successful, it could open up a host of opportunities for studying planarian biology and, in particular, how the organisms regenerate their brains. Ultimately, what scientists learn could help human brains recover from stroke or traumatic brain injuries.

Hall came across Melosh's work through an internet search for novel ways of transferring genetic material. The nanostraws he turned up are tiny, glass-like protrusions that use an electrical current to poke equally tiny holes in cell membranes to deliver their cargo. Perhaps, Hall thought, he could use nanostraws to get the material necessary for genetic modifications into planarian cells.

There was an added bonus. The internet search may have scoured the entire web, but the best idea came from a lab just a few buildings away from where Hall works. Hall cold-called Melosh, a professor of materials science and engineering, who by that time was already delivering some molecules into certain difficult-to-work-with human and mouse cells, and asked for help.

Soon after, Hall and Sergio Leal-Ortiz, PhD, a staff scientist in Melosh's lab, were applying nanostraws to Hall's planarian problem. Soon after that, they succeeded in getting genetic material inside adult planarian stem cells. Although there's room to improve in some planarian cell types, Hall said successes in other areas suggest that — by playing with nanostraw size, number and electrical properties — they should be able to make the technique viable in a wide variety of situations. "We are confident that there's a lot of optimization that can be done," Hall said.

RATTIYA THONGDUMHYU/SHUTTERSTOCK.COM

Using nanoscale straws, bioengineers and materials scientists are working to edit the genes of tiny flatworms called planarians.

Wang is optimistic, too. "Being able to genetically manipulate the worms would be a huge step," he said. "Once that opens up, there's so many things that you could do." For example, researchers could study other aspects of planarian biology, or apply similar methods to open up other organisms to genetic study.

"Crossing the boundaries of disciplines is so important," he said. "Without new technology, we're just stuck."

See FLATWORM, page 5

Breadth of student research showcased at annual symposium

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 and aspiring psychiatrist, he's helped to develop a genetically engineered mouse model that he and fellow researchers can use to investigate the underlying mechanisms thought to play a role in molecular learning and memory.

Sole was one of 60 medical students presenting posters of their work on April 30 at this year's Medical Student Research Symposium at the Li Ka Shing Center for Learning and Knowledge. The annual event, which showcases student research, is part of the Medical Scholars Research Program, a grant program started at the School of Medicine nearly 40 years ago. Medical students complete at least one quarter of research to fulfill their graduation requirements, yet many dedicate more time to longer-term projects.

Second-year medical student Sandrene Cassells, from Miami, has been studying how to systematically screen patients for 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.

"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 treatments," Cassells said. "And so, an ongoing battle is the idea that 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."

The doctors, medical assistants and social workers interviewed in Cassells' study cited potential barriers to this type of screening that included time constraints, reluctance to ask questions that might seem intrusive and concerns that patients' answers would not necessarily be actionable. Cassells' next steps are to develop and pilot an efficient screening tool for testing in a primary care setting.

Fifty judges

Each year, faculty and staff serve as judges for the event, and this year there were 50 of them. In her second year as a symposium judge and third year as a Med Scholars mentor, Reena Thomas, MD, PhD, clinical assistant professor of neurology and neurological sciences, said supporting students is one of her favorite aspects of the work. "It's been rewarding to serve as a mentor to students with distinct research interests and to build on their technical expertise through med school," she said. "This is truly one of the things that I love most, because I get to teach early-stage students who are just learning the ropes of medical school, and then — as they further develop in their clinical training — to apply this newly acquired knowledge to a translational research project."

For the 33 million people, including his own grandfather, who suffer from atrial fibrillation — the most common heart-rhythm disorder in the world — second-year medical student Kevin Cyr is taking a year off from his regular studies to develop a personalized device aimed at providing more precise diagnosis and treatment. "The current treatment options for atrial fibrillation have a one-size-fits-all approach," Cyr said. "And because of that, the success of these therapies has been really limited."

Cyr and his colleagues have designed a small silicone device, covered in 256 electrical receptors, that wraps partially around the heart. The devices, now being tested in an animal model of atrial fibrillation, are custom-built, since the configuration and size of every heart is unique. The receptors map electrical activity in the organ at high resolution, pinpoint the source of the atrial fibrillation and could potentially deliver the ablation necessary to treat it. In humans, the device would be temporarily placed around the heart during open surgery and removed before the surgery is concluded. Cyr and his team are also developing a minimally invasive approach that would allow the device to be placed and removed through a much smaller opening in the chest. "It could also be used as an advanced research tool to help us study atrial fibrillation in a lot more detail than we've ever been able to before," Cyr said.

At most scientific conferences, posters are organized by discipline, said Neil Gesundheit, MD, senior associate dean for medical education and professor of medicine. "You go to a cardiology meeting, or a meeting in critical care medicine or in my field of endocrinology, and all the posters are linked to that field. But at this event, you go poster by poster, and they jump from pharmacology to neuro-regeneration to cardiovascular disease to epidemiology of women's heart disease. It's an enormous diversity, reflecting the enormous variety of research topics that our students pursue, with faculty oversight."

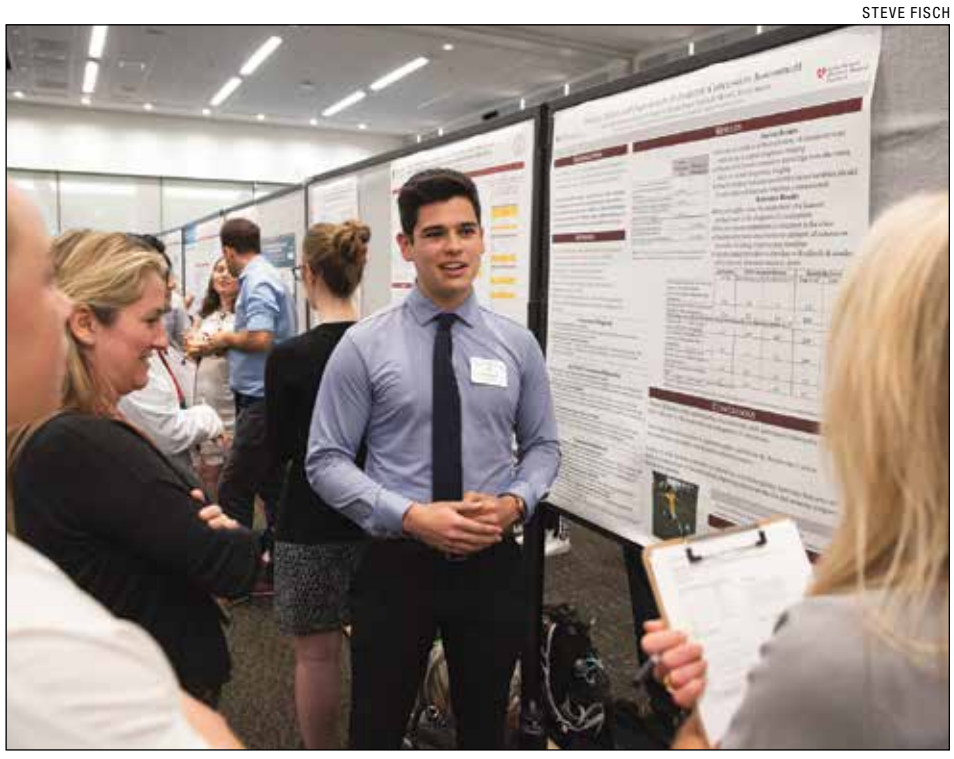
"It's been rewarding to serve as a mentor to students with distinct research interests."

Victor Carrion, MD, the John A. Turner, MD, Endowed Professor for Child and Adolescent Psychiatry, who was serving as a judge, agreed. "I'm very impressed by the broadness of subjects," he said, noting posters in biology, physiology, policy, genetics and even private practice. "I'm also very taken by how they're thinking interdisciplinarily. A lot of the posters present a view through different lenses of medicine, and that's a very good reflection of not only where we are in medicine now, but the environment here at Stanford."

Winning poster presentations:

- Sarthak Angal, "Emotional processing in depressed and anxious youth at high-risk for bipolar disorder." Mentor: Manpreet Singh, MD, associate professor of psychiatry and behavioral sciences.
- Razina Aziz-Bose, "Role of CRTAC1 and NGR in diffuse intrinsic pontine glioma invasion." Mentor: Michelle Monje, MD, associate professor of neurology.
- Kevin Cyr, "A novel patient-specific device for atrial fibrillation mapping, pacing and ablation therapy." Mentor: Anson Lee, MD, assistant professor of cardiothoracic surgery.
- Rashad Jabarkheel, "Intraoperative detection of pediatric brain tumor margins." Mentor: Gerald Grant, MD, professor of neuroscience.

STEVE FISCH



(Clockwise from top left) Tyler Bryant, left, discussed his poster presentation on April 30 with Vinicio de Jesus Perez, a judge at the Medical Student Research Symposium. Ivan Mayor presented his project, "Parental beliefs and expectations in pediatric concussion assessment." Sandrene Cassells discussed her research with judge Grant Miller.

- Julia Kao, "Mechanism of isocitrate impact on erythrocyte differentiation in iron-replete and deficient conditions." Mentor: Ravindra Majeti, MD, PhD, professor of medicine.
- Candice Kim, "Elucidating p63-mediated repression of keratin 18 during epithelial differentiation." Mentor: Anthony Oro, MD, PhD, professor of dermatology.
- Monica Liu, "Disparities in surgical intervention for colorectal cancer: A SEER analysis from 2000-2015." Mentor: Arden Morris, MD, PhD, professor of surgery.
- Pamela Meza, "A population-based study: Changing the landscape of obstetric care and resident education in LMIC using simulation-based training." Mentor: Kay Daniels, MD, clinical professor of obstetrics and gynecology. **ISM**

Flatworm

continued from page 4

Andrew Fire, the George D. Smith Professor in Molecular and Genetic Medicine and a professor of pathology and of genetics, is also contributing to the project. Fire is a member of Stanford Bio-X, the Stanford Maternal & Child Health Research Institute and the Stanford Cancer Institute. Wang is a member of Bio-X and the Wu Tsai Neurosciences Institute. Melosh is a member of Bio-X, the Maternal & Child Health Research Institute, the Precourt Institute for Energy at Stanford, Stanford ChEM-H and the Wu Tsai Neurosciences Institute. **ISM**

Autism

continued from page 1

some reductions in anxiety and repetitive behaviors.

"We saw this across multiple measures independently," Parker said. "It is really exciting."

STEVE FISCH

A placebo-controlled clinical trial led by Antonio Hardan and Karen Parker found that social skills in children with autism improved after they inhaled a hormone called vasopressin.

"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 repeated.

"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 Stanford. Large trials are also needed to assure the drug's safety.

Sex-specific social hormones

Vasopressin is a tiny protein hormone, nine amino acids long, manufactured 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 males, vasopressin influences pair-bonding and fathering behavior. Oxytocin regulates aspects of childbirth and certain maternal behaviors, such as milk letdown during nursing.

Oxytocin has been tested as an autism treatment with mixed results; Parker and Hardan previously showed that among autistic children whose oxytocin levels were low to begin with, giving that hormone improved aspects of social behavior. However, many children with autism do not have low oxytocin levels.

Vasopressin's social effects in males made the researchers wonder if this hormone influences autism. The disorder is male-biased, with 4 or 5 males affected for every female.

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 shown.

The Stanford team recruited 30 children with autism, all of whom were 6 to 12 years old and had an IQ of at least 50. The participants were randomly assigned, in a double-blind fashion, to receive intranasal vasopressin or a placebo. Participants took daily doses of their assigned medication for four weeks.

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. Children's repetitive behaviors and anxiety levels were also measured. The researchers also completed physical and clinical chemistry measurements to evaluate the safety of the treatment.

Children's social abilities improved more after vasopressin than placebo, according to the parents' and researchers' observations, as did children's performance on objective lab tests of social abilities. Vasopressin also reduced anxiety symptoms.

The changes in social ability and anxiety were greatest among children whose vasopressin levels were highest at the beginning of the study, a finding that surprised the researchers, given that their prior work had showed the lowest social abilities in children with the lowest vasopressin levels.

> "Identifying who responds and why is really important."

In addition, among children with the highest vasopressin at baseline, vasopressin treatment reduced restricted and repetitive behaviors. This finding did not extend to participants with lower baseline vasopressin.

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

If the findings of the pilot trial are replicated, it will also be important to validate the safety of the hormone in large populations and to understand which aspects of social behavior are most improved by vasopressin, Hardan 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 Oztan, PhD; clinical research coordinator Robin Libove; former life sciences researcher Noreen Mohsin; research scientist Debra Karhson, PhD; former assistant clinical research coordinator Raena Sumiyoshi; incoming medical resident Jacqueline Summers; Kyle Hinman, MD, clinical assistant professor of psychiatry and behavioral sciences; Kara Motonaga, MD, clinical associate professor of pediatrics; Jennifer Phillips, PhD, clinical associate professor of psychiatry and behavioral sciences; former postdoctoral scholar Dean Carson, PhD; Lawrence Fung, MD, PhD, clinical assistant professor of psychiatry and behavioral sciences; and Joseph Garner, DPhil, associate professor of comparative medicine.

Parker, Hardan, Fung and Garner are members of the Stanford Maternal & Child Health Research Institute. Parker, Hardan and Garner are also members of Stanford Bio-X and the Wu Tsai Neurosciences Institute at Stanford. Garner is a faculty fellow of Stanford ChEM-H.

The research was supported by the National Institutes of Health, Autism Speaks, a Bass Society Pediatric Fellowship, the Mosbacher Family Fund for Autism Research, the Teresa and Charles Michael Endowed Fund for Autism Research and Education, the Stanford Maternal & Child Health Research Institute and the Yani Calmidis Memorial Fund for Autism Research.

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

Biomarker

continued from page 1

him and Esfandyarpour to develop the new diagnostic tool.

The approach, of which Esfandyarpour led the development, employs a "nanoelectronic assay," which is a test that measures changes in miniscule amounts of energy as a proxy for the health of immune cells and blood plasma. The diagnostic technology contains thousands of electrodes that create an electrical current, as well as chambers to hold simplified blood samples composed of immune cells and plasma. Inside the chambers, the immune cells and plasma interfere with the current, changing its flow from one end to another. The change in electrical activity is directly correlated with the health of the sample.

> "There is scientific evidence that this disease is not a fabrication of a patient's mind."

The idea is to stress the samples from both healthy and ill patients using salt, and then compare how each sample affects the flow of the electrical current. Changes in the current indicate changes in the cell: the bigger the change in current, the bigger the change on a cellular level. A big change is not a good thing; it's a sign that the cells and plasma are flailing under stress and incapable of processing it properly. All of the blood samples from ME/CFS patients created a clear spike in the test, whereas those from healthy controls returned data that was on a relatively even keel.

"We don't know exactly why the cells and plasma are acting this way, or even what they're doing," Davis said. "But there is scientific evidence that this disease is not a fabrication of a patient's mind. We clearly see a difference in the way healthy and chronic fatigue syndrome immune cells process stress." Now, Esfandyarpour and Davis are expanding their work to confirm the findings in a larger cohort of participants.

Doubling up

In addition to diagnosing ME/CFS, the researchers 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/CFS still respond poorly to stress and generate a spike in electrical current, then the drug likely didn't work. If, however, a drug seems to mitigate the jump in electrical activity, that could mean 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/CFS, 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 approved by the Food and Drug Administration or will soon be broadly accessible to the public, which is key to fast access and dissemination should any of these compounds pan out.

Other Stanford authors of the study are research scientists Mohsen Nemat-Gorgani, PhD, and Julie Wilhelmy; and research assistant, Alex Kashi.

The study was funded by the Open Medicine Foundation. Davis is the director of the foundation's scientific advisory board.

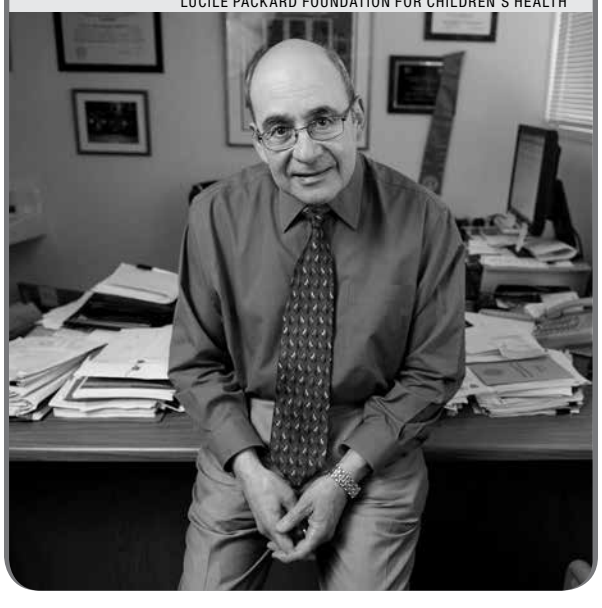
Stanford's departments of Genetics and of Biochemistry also supported the work. ISM

Memorial service for Oscar Salvatierra set for May 23

The Stanford community is invited to attend a memorial service for Oscar Salvatierra, MD, professor emeritus of surgery and of pediatrics 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 kidney transplant program at Lucile Packard Children's Hospital Stanford, was a leader in the effort to enact national legislation regulating organ donation. He died March 16. He was 83. ISM

LUCILE PACKARD FOUNDATION FOR CHILDREN'S HEALTH



OBITUARY

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

By Mandy Erickson

Roy Maffly, MD, former associate dean for student affairs at the Stanford University School of Medicine and a champion for recruiting underrepresented minorities to the school, died April 15 at his home in Palo Alto after a brief illness. He was 91.

Maffly was remembered most for his teaching and mentoring of medical students and residents. In 1982, he was the first instructor at the School of Medicine to receive the Walter J. Gores Award, the university's highest honor for excellence in teaching.

"He was a sensational dean and teacher to all the medical students," said Judith Nevitt, MD, a former student and now an adjunct associate professor in ophthalmology. "You always knew you could go to Dr. Maffly with a question or a thought. He was always kind and compassionate, always free with his time."

> "You always knew you could go to Dr. Maffly with a question or a thought."

Maffly helped establish a minority admissions committee, which he chaired from 1973 to 1977 and which is credited with diversifying the school's enrollment. He also proposed that the school allow flexible work schedules to accommodate students with children.

"Not only was Roy Maffly valued and respected as a teacher and mentor, he was a much-needed proponent for equality," said Lloyd Minor, MD, dean of the School of Medicine. "In the 1970s, Roy was instrumental in increasing admission of underrepresented minorities at the School of Medicine — understanding that better representation in medicine would help reduce disparities in health care."

Roy Maffly

Berkeley native

Maffly was born Nov. 26, 1927, in Berkeley, California, to a family with a long history in health care. His great-grandfather, Leroy Francis Herrick, also a physician, founded the former Herrick Memorial Hospital in Berkeley.

Maffly earned a bachelor's degree at UC-Berkeley in 1949 and a medical degree from UC-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.

He completed residencies at UCSF and at Herrick Hospital, where he was chief resident. He then served in the U.S. Naval Reserve Medical Corps from 1955 to 1957. He also served in the U.S. Army in 1946, when he was drafted into active duty as an undergraduate.

He completed two research fellowships, one at Massachusetts General Hospital and another at UCSF. His research, which involved toad bladders and the passage of sodium and potassium through cell walls, informed the treatment of heart and kidney diseases.

Maffly joined the Stanford faculty in 1961 as an assistant professor of medicine in endocrinology and metabolism. He was made a full professor in 1970 and became associate dean for student affairs in 1983. He retired in 1992.

"He was very committed to social issues," said his daughter Laurie Maffly-Kipp of St. Louis, Missouri. "He was influenced by the civil rights movement, and proud of his work on the minority commission. He tried to make underrepresented students feel more at home."

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 Jamison, 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 many 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. ISM

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.

Listening to 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.

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.

Peter Kim

Start now

Weidenbacher mentioned his idea to Kim after the talk, but both assumed someone else would have thought of such a simple idea. Then, Weidenbacher got a late-night email from Kim. "Peter was like, 'Nobody's done it; start now,'" said Weidenbacher, who joined Kim's lab through a ChEM-H graduate program that trains students to apply chemistry know-how to problems in biology and medicine.

"Payton is a chemist," Kim said. "What he did is come up with a way of using the monoclonal antibody not as something you look at but as a reagent."

Although the idea was simple, carrying it out was not. Weidenbacher encountered some hurdles getting the system to work, but the team's early tests, which they describe in a paper published April 26 in the *Proceedings of the National Academy of Sciences,* look promising.

Lab animals that received this cleverly cloaked flu 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.

Payton Weidenbacher

Kim and Weidenbacher said they've "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.

"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 Bio-X, the Stanford Maternal & 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 Zuckerberg Biohub.

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

Medical school faculty elected to National Academy of Sciences

Three School of Medicine researchers are among the 100 newly elected members of the National Academy of Sciences.

The new members are Karla Kirkegaard, PhD, the Violetta L. Horton Research Professor, and professor of genetics and of microbiology and immunology; Mark Krasnow, MD, PhD, the Paul and Millie Berg Professor of Biochemistry; and William Weis, PhD, William M. Hume Professor and professor of structural biology, of molecular and cellular physiology and of photon science.

Kirkegaard's work focuses on the impact of basic science discoveries on the transmission of viruses in infected hosts. She has combined her interests in biochemistry, cell biology and genetics in the study of RNA virology, using poliovirus and other positive-strand RNA viruses to understand the cell biology of viral infections and the genetics of viral variability.

Krasnow, who is also a Howard Hughes Medical Institute investigator, uses genetic and genomic approaches to elucidate the cellular and molecular basis of lung development and stem cells and the neural circuit of breathing. His research seeks to understand the normal processes and how they go awry in human diseases such as lung cancer, pulmonary fibrosis, pulmonary hypertension and sudden infant death syndrome.

Weis studies molecular interactions that underlie the establishment and maintenance of cell and tissue structure using biochemical and biophysical methods. His lab's specific areas of interest are the architecture and dynamics of intercellular adhesion junctions and signaling pathways that govern cell fate determination. The team also investigates carbohydrate-based cellular recognition and adhesion.

Karla Kirkegaard

Mark Krasnow

William Weis

The academy is a private, nonprofit institution that was created in 1863 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. ISM

Tad and Dianne Taube commit $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 cancer.

"It is essential that we help society's most vulnerable, our children, to beat cancer," said Tad Taube, chairman of Taube Philanthropies. "Researchers at Stanford, one of the world's preeminent research institutions, are leading the way in the search for better treatments for this dreadful disease. We are proud to support them in their effort to save countless children's lives."

The gift will accelerate the work of researchers at the School of Medicine and Lucile Packard Children's Hospital Stanford who are exploring promising areas of discovery, such as cancer genomics and immunotherapy. It will support two faculty members performing cutting-edge cancer research in key areas and establish a fund for future innovation.

"Through their generous contribution, 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 incurable 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:

- $20 million to help open the Tad and Dianne Taube Pavilion at Packard Children's new main building.
- $9.5 million to establish the Tad and Dianne Taube Youth Addiction Initiative.
- $5 million to create the Taube Stanford Concussion Collaborative, which advances education, care and research to protect children from concussions.
- $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. **ISM**

SUSANA BATES FOR DREW ALTIZER

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

OF NOTE

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

MARCELLA ALSAN, MD, PhD, associate professor of medicine, is co-recipient of the 2019 Kenneth J. Arrow Award from the International Health Economics Association. She and Marianne Wanamaker, PhD, of the University of Tennessee won the award for "Tuskegee and the Health of Black Men," a paper published in the *Quarterly Journal of Economics.* The award recognizes excellence in health economics and is named for the late Nobel laureate and Stanford economist.

JACOB BLYTHE, a third-year medical student, was awarded a 2019 medical fellowship from the Fellowships at Auschwitz for the Study of Professional Ethics. He will travel to Germany and Poland this summer to participate in a two-week program that focuses on contemporary professional ethics in light of the conduct of physicians in Nazi-occupied Europe.

JEFFREY GOLDBERG, MD, PhD, professor and chair of ophthalmology, and **ANDREW HUBERMAN**, PhD, associate professor of neurobiology and of ophthalmology, have each received grants from the Gilbert Family Foundation's Vision Restoration Initiative to accelerate the development of therapies for neurofibromatosis type 1, a rare disease characterized by symptoms including optic gliomas, which are benign tumors that can lead to optic nerve damage and vision loss. The awards, totaling $3 million, will fund their efforts to advance therapies for protecting and restoring retinal ganglion cells and vision in neurofibromatosis type 1-associated optic gliomas.

AIDA HABTEZION, MD, associate professor of gastroenterology and hepatology, was awarded a $1 million grant from the Leona and Harry B. Helmsley Foundation for a feasibility study assessing myoelectric activity patterns in Crohn's disease patients during flares and remission.

MARY HAWN, MD, MPH, the chair of surgery and the Stanford Medicine Professor of Surgery, was elected secretary of the American Surgical Association. It is a five-year appointment.

REBECCA RICHARDS, MD, PhD, a fellow in pediatric hematology/oncology, will receive a grant for $195,000 from the St. Baldrick's Foundation. The award will support her efforts to develop CAR-T cells targeting the CD93 protein for treatment of acute myeloid leukemia.

LAURA ROBERTS, MD, professor and chair of psychiatry and behavioral sciences and the Katharine Dexter McCormick and Stanley McCormick Memorial Professor, has been voted president-elect of the American College of Psychiatrists.

TAIT SHANAFELT, MD, the Jeanie and Stew Ritchie Professor, professor of medicine, chief wellness officer and associate dean, received an honorary fellowship from the American Association for Physician Leadership. He was recognized for his pioneering research into and advocacy for physician well-being over the past 20 years, and for helping create the field of organizational and systems approaches to physician wellness.

ROBERT TIBSHIRANI, PhD, professor of biomedical data science and of statistics, was elected a fellow of The Royal Society, the world's oldest independent scientific academy. He was recognized for his seminal contributions to the fields of bioinformatics and statistics, namely his invention of statistical tools for extracting information from data. **ISM**

Marcella Alsan

Jacob Blythe

Jeffrey Goldberg

Andrew Huberman

Aida Habtezion

Mary Hawn

Rebecca Richards

Laura Roberts

Tait Shanafelt

Robert Tibshirani

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. **ISM**